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Redox Status Training and Detraining Responses in Low-Risk Heart Disease Patients Following Aerobic, Resistance and Combined Exercise Training

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ΠΡΟΣΑΡΜΟΓΕΣ ΚΑΙ ΑΠΟΠΡΟΣΑΡΜΟΓΕΣ ΤΗΣ ΑΕΡΟΒΙΑΣ ΑΣΚΗΣΗΣ, ΤΗΣ ΑΣΚΗΣΗΣ ΑΝΤΙΣΤΑΣΕΩΝ ΚΑΙ ΤΟΥ ΣΥΝΔΥΑΣΜΟΥ ΤΟΥΣ ΣΤΗΝ ΟΞΕΙΔΟΑΝΑΓΩΓΙΚΗ ΚΑΤΑΣΤΑΣΗ ΚΑΡΔΙΟΠΑΘΩΝ ΧΑΜΗΛΟΥ ΚΙΝΔΥΝΟΥ

του

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ΠΕΡΙΛΗΨΗ

Τρύφωνας Κ. Τόφας: Προσαρμογές και αποπροσαρμογές της αερόβιας άσκησης, της άσκησης αντιστάσεων και του συνδυασμού τους στην οξειδοαναγωγική κατάσταση καρδιοπαθών χαμηλού κινδύνου.

(Με την επίβλεψη του Καθηγητή Τζιαμούρτα Αθανάσιου)

Έχει πλέον τεκμηριωθεί βιβλιογραφικά ότι η χρόνια / τακτική άσκηση μειώνει το οξειδωτικό στρες και αυξάνει τους αντιοξειδωτικούς δείκτες σε ασθενείς με καρδιαγγειακή νόσο. Ωστόσο, επί του παρόντος, δεν υπάρχουν επαρκείς πληροφορίες σχετικά με τον τρόπο με τον οποίο αποκρίννονται αυτοί οι δείκτες μετά από διαφορετικού τύπου άσκησης καθώς επίσης και μετά από τη διακοπή ενός προγράμματος άσκησης. Ο σκοπός της παρούσας μελέτης ήταν να εξεταστούν οι μεταβολές της οξειδοαναγωγικής κατάστασης ασθενών με στεφανιαία νόσο, κατά τη διάρκεια, μετά το τέλος και μετά από τρίμηνη διακοπή τριών διαφορετικών προγραμμάτων άσκησης (αερόβιας προπόνησης, άσκησης με αντιστάσεις και συνδυαστικής προπόνησης).

Στην παρούσα έρευνα συμμετείχαν πενήντα έξι ασθενείς με στεφανιαία νόσο, οι οποίοι καταμερίστηκαν τυχαία σε τέσσερις ομάδες: α) ομάδα αερόβιας άσκησης (n=15) β) ομάδα άσκησης αντιστάσεων (n=11), γ) ομάδα συνδυαστικής άσκησης (n=15) και δ) ομάδα ελέγχου (n=15). Οι συμμετέχοντες στις τρεις ομάδες άσκησης υποβλήθηκαν ανάλογα με την περίπτωση σε παρεμβατικό πρόγραμμα άσκησης διάρκειας 8 μηνών, 3 ημέρες την εβδομάδα. Πριν, κατά τη διάρκεια ($4^{ο}$ μήνα), αμέσως μετά το τέλος του παρεμβατικού προγράμματος άσκησης ($8^{ο}$ μήνα), καθώς επίσης και μετά τη διακοπή του παρεμβατικού προγράμματος (στον $1^{ο}$, $2^{ο}$ και $3^{ο}$ μήνα) αξιολογήθηκαν η μέγιστη αερόβια ικανότητα (VO2max), η μέγιστη ισομετρική μυϊκή δύναμη (Nm), η ευκαμψία καθώς επίσης και η οξειδοαναγωγική κατάσταση [δραστικές ουσίες θειοβαρβιτουρικού οξέος (TBARS), ολική αντιοξειδωτική ικανότητα (TAC), ανηγμένη γλουταθειόνη (GSH), οξειδωμένη γλουταθειόνη (GSSG) πρωτεϊνικά καρβονύλια (PC)] των συμμετεχόντων.

Μετά από οκτώ μήνες άσκησης, παρουσιάστηκαν ευνοϊκές επιδράσεις στις παραμέτρους φυσικής κατάστασης (VO2max, μυϊκή δύναμη και ευκαμψία) καθώς επίσης και στην οξειδοαναγωγική κατάσταση των ασθενών. Η αερόβια προπόνηση φάνηκε να επηρεάζει θετικά και για μεγαλύτερο χρονικό διάστημα σχεδόν όλες τις μεταβλητές του οξειδωτικού στρες (TBARS, TAC, GSH, GSSG, CAT και PC) τις οποίες αξιολογήσαμε, η συνδυαστική άσκηση επηρέασε θετικά μέρος των οξειδωτικών και αντιοξειδωτικών μεταβλητών (TBARS, TAC, CAT και PC) ενώ η άσκηση αντιστάσεων επηρέασε θετικά τις λιγότερες μεταβλητές οξειδωτικού στρες (TAC, CAT, PC). Κατά την περίοδο διακοπής του προγράμματος, σχεδόν

όλοι οι δείκτες οξειδωτικού στρες για όλες τις ομάδες, επανήλθαν στα αρχικά τους επίπεδα, εκτός από τις συγκεντρώσεις GSSG και CAT στην ομάδα αερόβιας άσκησης.

Τα ευρήματά αυτά μας δείχνουν ότι ο τύπος και η ένταση της άσκησης φαίνεται να παίζουν σημαντικό ρόλο στις αλλαγές στα αντιοξειδωτικά ένζυμα. Υποστηρίζουν επίσης ότι η αερόβια άσκηση σχετίζεται με υψηλότερη αντιοξειδωτική ικανότητα. Τρεις μήνες διακοπής ενός παρεμβατικού προγράμματος είναι αρκετοί για να καταργήσουν πλήρως τις ωφέλιμες επιδράσεις που προκαλούνται από την άσκηση στην οξειδοαναγωγική κατάσταση των ασθενών, γεγονός που συνιστά ότι για μια καλύτερη αντιοξειδωτική κατάσταση, η άσκηση πρέπει να γίνεται εφόρου ζωής.

Λέξεις-κλειδιά: καρδιαγγειακές παθήσεις, οξειδωτικό στρες, αερόβια άσκηση, άσκηση αντιστάσεων, συνδυαστική προπόνηση.

ABSTRACT

Tryfonas C. Tofas : Redox Status Training and Detraining Responses in Low-Risk Heart Disease Patients Following Aerobic, Resistance and Combined Exercise Training

(Under the supervision of Athanasios Jamurtas, Professor)

It has been documented that chronic/regular exercise decreases oxidative stress and increases antioxidant capacity in cardiovascular disease patients. Nevertheless there is insufficient information on how these markers respond due to participation in a prolonged exercise training program with different modes of exercise and what the detraining responses are after the termination of such a program. Thus, the purpose of the present study was to determine the effects of aerobic, resistance and combined exercise training followed by a three months detraining period on redox status in cardiovascular diseases patients. Fifty six coronary artery disease patients, were randomly assigned to aerobic exercise training (AT, n = 15), resistance exercise training (RT, n = 11), combined exercise training (CT, n = 15) and control (C, n = 15) groups. The exercise training groups, participated in a supervised training program, 3 days a week for 8 months. Aerobic capacity (VO2max), muscular strength, flexibility and redox status related variables [thiobarbituric acid reactive substances (TBARS), total antioxidant capacity (TAC), reduced glutathione (GSH), oxidized glutathione (GSSG), catalase activity (CAT), protein carbonyls (PC)] were assessed at the beginning of the study, after 4 and 8 months of training and 1, 2 and 3 months of detraining. Eight months of exercise training showed favorable effects of the training on physical fitness parameters (VO2max, muscular strength and flexibility) and redox status. The aerobic exercise training affected positively and over a longer period of time all the oxidative stress variables (TBARS, TAC, GSH, GSSG, CAT and PC) that we were assessed, whereas combined exercise training affected positively some variables (TBARS, TAC, CAT and PC) whereas resistance exercise training affected positively only few oxidative stress variables (TAC, CAT, PC). Almost all biomarkers of oxidative stress for all groups restored near the pre exercise values at the end of the supervised exercise program, except GSSG and CAT in the aerobic exercise group.

Our findings suggest that the type and the intensity of exercise, seem to play an important role on the redox status of coronary artery patients. It is also suggested that aerobic exercise training results in more pronounced positive results on redox status parameters. Three months of detraining is enough to completely abolish the exercise-induced beneficial effects on redox status, thus, it shows that for a better antioxidant status, exercise must be a lifetime commitment.

Key words: cardiovascular diseases**,** oxidative stress, aerobic exercise, resistance exercise, combined exercise, detraining.

Στη γυναίκα μου Αθηνά
και στις δυο μου κόρες Έλλη και Κωνσταντίνα!

ΕΥΧΑΡΙΣΤΙΕΣ

Φτάνοντας στο τέλος της συγγραφής της παρούσας διατριβής, θα ήθελα να εκφράσω την ειλικρινή μου ευγνωμοσύνη στους ανθρώπους που χωρίς την παρουσία, την υποστήριξή και κυρίως την ανεκτικότητα τους δεν θα ήταν δυνατή η υλοποίηση της.

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Θερμές ευχαριστίες στον Δρ. Τοκμακίδη Σάββα ως μέλος της τριμελούς επιτροπής, για τον συμβουλευτικό του ρόλο, καθώς και τον Δρ. Φατούρο Ιωάννη, που δέχτηκε να τον αντικαταστήσει μετά τη συνταξιοδότησή του, ως μέλος της τριμελούς επιτροπής. Η συμβολή του Δρ. Φατούρου ήταν πολύ σημαντική και η ολοκλήρωση του διδακτορικού μου οφείλεται σε μεγάλο βαθμό σε αυτόν, γιατί έδωσε λύση για την πραγματοποίηση μεγάλου μέρους των βιοχημικών αναλύσεων της διατριβής μου στο εργαστήριο του, γι' αυτό και τον ευχαριστώ μέσα από την καρδιά μου.

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Επίσης, θέλω να πω πολλά ευχαριστώ, στο φίλο Χάρη Τζιωρτζή, ο οποίος συνέβαλε τα μέγιστα στην υλοποίηση του παρεμβατικού προγράμματος της άσκησης και τον κ. Φιλόκυπρο Χριστοδούλου, ο οποίος έκανε τις αιμοληψίες κατά τη διάρκεια των αξιολογήσεων. Ευχαριστώ επίσης, τον Δρ. Παναγιώτου Γιώργο από το Ευρωπαϊκό Πανεπιστήμιο Κύπρου, για το συμβουλευτικό του ρόλο κατά τη διάρκεια του παρεμβατικού

προγράμματος και για την πολύτιμη βοήθεια του κατά τη διάρκεια των αξιολογήσεων της φυσικής κατάστασης των ασθενών.

Θα ήθελα ακόμη να εκφράσω την ευγνωμοσύνη μου στους γονείς μου, Κώστα και Ελένη, για την αγάπη και τη στήριξη τους αλλά και που μου έδωσαν την ευκαιρία κάτω από δύσκολες συνθήκες, να σπουδάσω αυτό που πραγματικά αγαπώ.

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I. INTRODUCTION

Over the years, different studies have reported improvements in cardiovascular health and quality of life, by following physical exercise intervention in CVD patients. Exercise clearly provides health benefits to humans that subsist even with short sessions beneath the recommended intensity and duration. Short training periods, reduce inflammatory markers, decrease atherosclerotic plaque and blood pressure and improve lipid profile, due to the antioxidant and anti-inflammatory effects of exercise.

These beneficial consequences of regular exercise are in sharp contrast to the effects of physical inactivity and exhaustive exercise on unprepared tissues that results in, apparently, harmful outcomes. A previous study indicated that, muscle damage induced by acute bout of exercise, is partly related to inflammation via phagocyte infiltration caused by ROS (Aoi ett al. 2004). Moreover, exhaustive exercise as well physical inactivity can produce a large quantity of ROS due to a dramatic increase in oxygen up taken at both the whole body and the local tissue level. Bloomer et al. (2007) found that post-exercise plasma of protein carbonyl concentration following a 120-min exercise bout (70% VO2max) was greater than that following 30 or 60 min exercise in young individuals, suggesting that oxidative stress is greater following a longer duration exercise.

There are conflicting results regarding the effects of exercise on oxidative stress. After an exercise programme, oxidative stress markers were found to be decreased (Silva et al. 2017), increased (Fatouros et al. 2010; Nikolaidis, et al. 2007; Aoi et al. 2004), or remained unchanged (Venojärvi M et al 2013).

Although several studies confirm the benefits of regular physical exercise on oxidative stress, it has also been shown that an acute physical exercise with a certain high intensity and duration, may induce an increase in the production of ROS. However, a repeated bout of exercise, attenuated muscle damage and blood oxidative stress, compared to the first bout (Nikolaidis, et al. 2007).Exercise training is an efficient way of reducing the susceptibility of muscles to further exercise-induced damage and several studies have suggested that, this protection is associated with an increased activity of muscle antioxidant enzymes, including superoxide dismutase, catalase and glutathione peroxidase as well as antioxidants such as vitamin C, vitamin E, carotenoids and glutathione (Higuchi et al. 1985; Robertson et al. 1991; Sen & Hanninen, 1994).

Moderate aerobic exercise training is the most preferred way of exercise, but patients can also benefit from moderate RE training. Therefore, these exercise prescription recommendations have been proposed to be the most appropriate for CVD patients.

Recent studies have suggested that intense exercise alternating moderate exercise during a session, is safe and well tolerated in CVD patients, and the benefits which are caused by more intense exercise seem to be better than those achieved by moderate exercise (Negrao et al. 2015). According to Arena and colleagues (Arena et al. 2013) high-intensity-aerobic interval training, can be safely performed, impressively improving physiology, functional capacity and quality of life. It is obvious from the recently published studies that both aerobic (Kim C et al. 2016), resistance (Jewiss D et al. 2016) exercise training, or a combination of the two in the same training session (Atashak Set al. 2016), are important and very effective for CVD patients.

Furthermore, it is widely described that chronic exercise reduces oxidative stress and damage, by both decreasing ROS production and increasing antioxidant capacity as well as improving mitochondria efficiency in several organs and systems. Park and colleagues (Park, 2016) suggested that any type of exercise training will be beneficial for improving redox balance against potential cardiovascular risk factors caused by excessive ROS. Furthermore, different oxidative stress biomarkers are affected by different exercise intensities and modes so that, instead of classical AE or RE training protocol, it seems to be more beneficial for the CVD patients the use of a combination of different intensities and modes in a training unit.

It is likely that, aerobic fitness is related to higher antioxidant capacity. In addition, aerobic exercise can trigger exercise-associated adaptive responses through metabolic and redox challenges (Radak et al., 2013; Ferraro et al., 2014; Wiggs, 2015).The decrease in oxidative damage associated with exercise training, could be also explained by an increase in antioxidant and metabolic efficiency, which possibly prevents the stimulation of DNA repair enzyme activity (Soares et al. 2015). These findings enhance the importance of regular exercise in the prevention of DNA damage accumulation, which has been related to aging (Nalapareddy et al. 2008) and some age-related diseases including cardiovascular disease (Collins et al. 1998). Furthermore, both chronic aerobic (Radak et al. 2009; 2013) and resistance exercise (Porter C et al. 2015) improve muscle mitochondrial density, as well as decrease oxidative stress in different tissues (Beltran Valls et al. 2014; Trost et al. 2005; Alessio 1993).

The long lasting effects of exercise on oxidative stress and its relationship with cardiovascular diseases is controversial, mainly because of the differences among the type, intensity, frequency and duration of the exercise programmes found in the literature. However, most of the studies concerned with physical exercise and related oxidative stress, have concentrated on the effects of AE (Done AJ & Traustadóttir T. 2016; Alghadir et al. 2016; Roque et al. 2013), RE (Parise et al. 2005; Vincent et al. 2006) or a combined exercise training (Soares et al. 2015; Azizbeigi et al. 2014; 2015) on oxidative stress mainly in healthy individuals.

Exercise training-mediated redox adaptations, occur through activation of signaling pathways that lead to increased synthesis of enzymatic and nonenzymatic antioxidants that maintain the 'physiological' reactive oxygen species (ROS) levels, where they can act as signaling molecules (Samjoo, 2013). In contrast to the redox adaptations which occur in response to exercise training, there is limited data about the detraining effects on oxidative stress markers.

It has been documented that chronic/regular exercise, decreases oxidative stress and increases antioxidant markers in CVD patients. Nevertheless, at present, there is insufficient information on how these markers act by an interruption in training due to illness, holidays etc. In addition, until now there was no information regarding weather the three exercise modes (aerobic, resistance and combined) have different effects on oxidative stress markers after a detraining period.

Most detraining studies have focused on the effects on muscular strength (Coetsee and Terblanche 2015; Yasuda et al. 2015; Harris et al. 2007; Fatouros et al. 2005, Toraman 2005), lipid metabolism (Theodorou et al. 2016; Farias et al. 2015; Zhu et al. 2015; Sertie at al. 2015; Mazzucatto et al. 2014; García-Hermoso et al. 2014; Mitsuhashi et al. 2011;), body mass index (Ormsbee and Arciero 2012; Mitsuhashi et al. 2011;), bone mineral density (Frotzler et al. 2009; Nordström et al. 2005; Valdimarsson et al.2005;Kudlac et al. 2004), functional fitness (Bocalini et al. 2010; Carvalho et al. 2009; Toraman and Ayceman, 2004; Toraman 2004), memory function (Kim et al. 2013) and cardiovascular response (Waring et al. 2015; Rodrigues et al . 2014; Stebbings et al. 2013; Spence et al. 2011; Lobo et al. 2010; Kemi et al. 2004; Raven and Shi 1995). Nevertheless, it remains unclear whether training adaptations persist (Coetsee and Terblanche 2015, Koshiba and Maeshima 2015; Nascimento et al. 2014; Carneiro-J_unior et al. 2010; Lehnen et al. 2010; Fatouros et al. 2005), or whether they are completely loss (Waring et al. 2015; Stebbins et al. 2013;

Carneiro-J_unior et al. 2013; Weiner et al. 2012; Bocalini et al. 2010; Kemi et al. 2004) after a small detraining period.

To the best of our knowledge, no previous study has evaluated the effect of exercise training followed by a detraining period on oxidative stress markers in cardiovascular diseases patients. Only Agarwal et al. (2012), investigated the detraining effects on oxidative stress, however the detraining period was too small and the subjects participated in this study were rats.

The purpose of the present study was to determine the effects of aerobic, resistance and combined exercise training followed by a three months of detraining period on oxidative stress markers in cardiovascular diseases patients.

II. LITERATURE REVIEW

2.1. Introduction

Considerable data indicate that free radicals and oxidative stress are significant aetiological factors for several degenerative diseases (Cerne D, Lukac-Bajalo J. 2006), such as cardiovascular diseases (Csonka et al. 2016; Molavi B, Mehta JL, 2004; Sugamura & Keaney, 2011; Strobel NA, et al., 2011; Chen AF, et al. 2012; Chen K, Keaney JF Jr, 2012), atherosclerosis (Usberti M, et al. 2002; Voghel G, et al. 2007), obesity, type 2 diabetes mellitus (Yan M, et al. 2011; Selvaraju V, et al. 2012), cancer (Crujeiras AB et al. 2013), neurological diseases of aging (Serra JA, et al. 2009; Miller VM, et al. 2009) and so on.

Oxidative stress is defined by the imbalance between the production of reactive oxygen species (ROS) and the endogenous antioxidant mechanisms to counteract the effects of ROS or repair the resulting damages (Lee et al. 2012). ROS are chemically reactive molecules derived from molecular oxygen and formed as natural by-product of aerobic metabolism (Taverne et al., 2013).

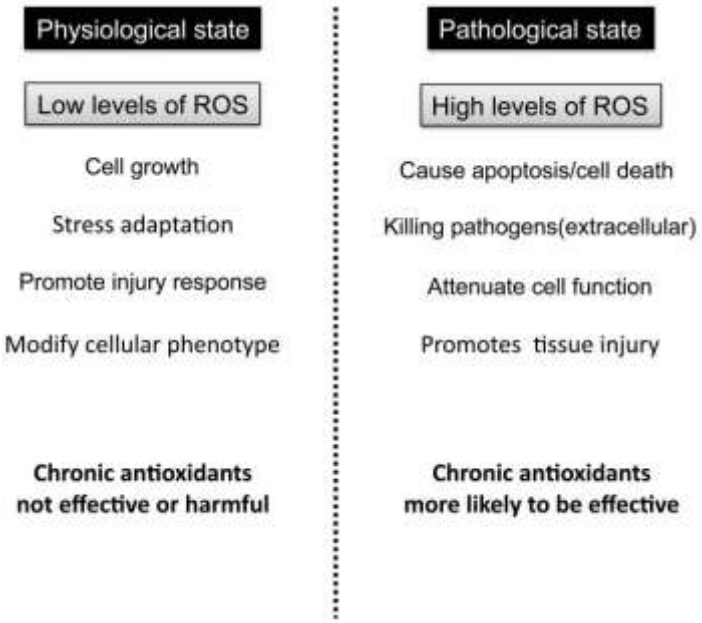


Figure 1: *Roles of ROS in physiological vs. pathological states.*

However, ROS playan important role in pathophysiology as well as in physiology (Sugamura & Keaney, 2011, Taverne et al., 2013, Papacharalambous & Griendling, 2007). All vascular cell types, including endothelial fibroblasts and resident macrophages, produce ROS (Touyz, 2004). Under physiological conditions, ROS concentrations are controlled by antioxidants. Low levels of ROS are necessary for normal vascular function. Specifically, there are evidences that low concentrations of ROS, can function as specific second messengers for cellular signal transduction and the balance between oxidizing and reducing species is known to be an important component of cellular homeostasis (Sugamura & Keaney, 2011) figure 1. On the

other hand, high levels or excess production of ROS, oxidize various molecules, causing damage onto lipids, proteins and DNA.

Furthermore, Roebuck (1999), Aoi et al. (2004), Meyer et al. (1994), suggested that oxidative stress, not only directly causes damage by oxidation of cell components such as lipids, proteins, and DNA, but also acts as a regulator of inflammation. This intracellular reduction-oxidation imbalance, in a proinflammatory environment, regulates virtually all of the cellular responses to injury, including monocyte adhesion; platelet aggregation; inflammatory gene induction; VSMC apoptosis, proliferation and migration; matrix degradation and impaired endothelium-dependent relaxation. All these evidence, demonstrate that oxidative stress plays an important role in the pathogenesis and development of cardiovascular diseases including atherosclerosis, ischemia-reperfusion injury, chronic ischemic heart disease, cardiomyopathy, heart failure, hypertension, dyslipidemia, diabetes mellitus, myocardial infraction, angina pectoris, and even ensuing arrhythmias (Taverne et al., 2013, Yukihito Higashi et al. 2009, Schnackenberg, 2002).

Although it has been established that oxidative stress plays major role in the development of CVDs, large intervention trials studies have failed to conclusively show any benefit after antioxidant supplementation in preventing or treating CVDs. One of the reason is that ROS are not universally harmful; repeated, low – level exposure to ROS is a vital trigger for up-regulation of endogenous antioxidants (Goszcz et al. 2015). Therefore, researchers have directed their attention towards nonpharmacological therapy in order to reduce oxidative stress with physical exercise has attracted a great interest. It is widely known that, oxidative stress is associated with CVDs and both of them can be influenced by physical exercise. The present review provides an overview of oxidative stress followed by a discussion of oxidative stress in relation to the antioxidant role of exercise for the cardiovascular diseases.

2.2. Oxidative stress and cardiovascular disease

CVD and endothelial dysfunction are characterized by a chronic inflammation and oxidative stress (Zembron-Lancy et al. 2016; Siti et al. 2015). As we said before, oxidative stress plays a double role in the pathogenesis and development of most cardiovascular diseases (CVDs). The pathogenesis of oxidative stress in the elderly can predispose the heart to other cardiac complications such as atherosclerosis, hypertension, ischemic heart disease, cardiac myopathy, and so on (Narasimhan et al. 2016).

Elevated oxidant levels have been shown to contribute to vascular dysfunction both in animal models and clinical studies (Fetterman JL et al. 2016, Ungvari Z et al. 2010, Harrison et al. 2003, Schulz et al. 2004). According toUngvari Z et al. (2010), ROS-mediated activation of retrograde signaling pathways, including NF-κB, lead to chronic low-grade vascular inflammation promoting the development of vascular diseases in the elderly.

Furthermore, Machi et al. (2016) suggested that impairment of heart function, may be related to increased oxidative stress in the tissue. ROS signaling plays an important part in endothelial function, vascular tone, and cardiac function. Conversely, when excessively produced, ROS can disrupt cellular signaling and inflict cellular damage (Taverne et al. 2013).

In addition, Kota et al. (2016) supported that, oxidative stress and inflammation triggered signals can either directly cause injury to the cardiac tissues or increase the atherosclerotic process. Furthermore, in pathological conditions such as in cardiovascular diseases, where generation of ROS is increased and the renin angiotensin system may upregulated, these redox-sensitive events may contribute to cellular processes involved in vascular dysfunction and structural remodeling (Touyz, 2004).

Oxidative stress induces cell proliferation, hypertrophy, apoptosis and inflammation through activation of various signaling cascades and redox-sensitive transcriptional factors. Excess ROS, especially free radicals, oxidize various molecules. Lipid peroxidation and protein oxidation induce overexpression of redox genes, intracellular calcium overload, and DNA fragmentation, causing damage to vascular smooth muscle cells (VSMCs), endothelial cells or myocardial cells. A vicious cycle of oxidative stress and oxidative stress-induces atherosclerosis, lead to the development of atherosclerosis (Higashi et al. 2009). A previous study suggested that, oxidized low-density lipoprotein, plays a key role in the development of atherosclerosis (Steinberg et al. 1997). Lipid peroxidation is believed to be involved in the peroxidative modification of LDL (Amrita et al. 2016, Schulz et al. 2004, Stringer et al. 1989, Plachta et al. 1992). Moreover, Zembron-Lancy et al. (2016), have shown that the levels of

oxidized low density lipoprotein (oxLDL), PC and lipid peroxidases (LPO) were elevated in elderly men and highly correlated with common CVD factors such as LDL, HDL and Framingham score.

Furthermore, measurement of circulating biomarkers of oxidative stress is challenging, since circulation usually behaves as a separate compartment to the individual structures of the vascular wall (R Lee et al. 2012). It has been noticed that several plasma biochemical markers of oxidative stress were increased in cardiovascular diseases patients (Aluganti Narasimhulu et al. 2016). Plasma levels of oxidized low-density lipoprotein are considered to be a prognostic indicator of mortality in subjects with congestive heart failure (Tsutsui et al. 2002, Narasimhulu et al. 2016). Moreover, many of the biomarkers of oxidative stress is used as a prognostic tool assessing the risk of cardiovascular disease (Amrita et al. 2016, R Lee et al. 2012). Serum lipid hydroperoxides, plasma malondialdehyde (MDA) or urine F2-isoprostanes are widely used and have a predictive value in cardiovascular disease. A recent study, has shown a significant increase in MDA and LDL carbonyl protein and a significant decrease in the activity of antioxidant enzyme, SOD, in cardiovascular disease menopausal women as compared to non – cardiovascular disease women (Amrita et al. 2016).

As we know, multiple factors are involved in the etiology of CVDs, and oxidative stress is one of them. Treatments that block the damaging effects of oxidative stress have long been considered as potential strategies to reduce cardiovascular disease. In order to reduce or prevent the adverse effects of oxidative stress in the organism, substances with antioxidant properties can be applied.

2.3. Antioxidants, Cardiovascular disease and Oxidative stress

Antioxidants are substances that “neutralize” before they are able to react with cellular components and alter their structure or function (Goszcz et al. 2015). Humans have evolved highly complex antioxidant systems (enzymatic and non-enzymatic) that work synergistically, and in combination with each other, so as to protect cells and organ systems of the body against free radical damage (Chen et al. 2012). Antioxidants can be either endogenously produced substances or obtained from exogenous sources e.g. as part of a diet or as dietary supplements (Kushwaha S et al. 2014, Schmidt HH et al. 2015, Bouayed J, Bohn T, 2010).

As we know, antioxidant offers protection against a wide spectrum of diseases. Antioxidants neutralize free radicals, provide cellular protection and fight against cardiovascular diseases. However, results from many interventional trials using oral antioxidants given as

supplements,have not been concordant with previous findings from observational epidemiologic cohort studies (Núñez-Córdoba JM, Martínez-González MA, 2011).

According to a review by Chen et al. (2012), oral antioxidant supplements have been ineffective as either preventative or therapeutic agents in CVDs. Furthermore, associations between plasma concentrations of antioxidant vitamins (A, C and E) and protection against cardiovascular disease have proved to be elusive and large intervention trials which used these vitamins have failed to conclusively show any benefit (Goszcz et al. 2016).

As we said before, oxidative stress is considered to be one of the main causative factors in various cardiovascular disorders, whereasexercise training has been cited as a non-pharmacological tool to prevent or treat many cardiovascular diseases (CVD) and seems to have an important role in oxidative stress. However, chronic exercise may not neutralize free radicals, but induces adaptations which enhance endogenous activitywhich can also be classified as the best antioxidant. Antioxidant enzymes provide the first line of cellular defense against ROS that cause oxidative stress (Hao 2014; Huang; Zhu et al. 2008). Primary antioxidant enzymes include superoxide dismutase (SOD), gludathione peroxidase (GPx) and catalase (CAT). Accumulated evidence has shown that increased antioxidant enzyme activity as well as increased resistance to oxidative stress, may protect against oxidative stress related damage to tissues and to cellular macromolecules (Hao, 2014, Chen Z. et al. 2013).

Relevant literature documents that, both aerobic, anaerobic and resistance training, cause an enhancement in the antioxidant enzymes activity in various tissues (da Palma RK et al. 2016, Gomes EC, 2012, Møller P et al. 1996). On the other hand, several studies have reported a significant decrease in SOD, GPx, and CAT activity after exhaustive high intensity exercise (Li et al. 2015; Hao, 2014; Yan et al. 2014). Nevertheless, the levels of oxidative stress depend on the intensity, duration and mode of the exercise training. In addition, exercise intensity and duration are critical determinants of cardiovascular beneficial effects (Garelnabi et al. 2014; Thijssen et al. 2012; Rankin et al. 2012).

In an effort to make some sense of the range of outcomes achieved with exercise regarding oxidative stress in CVDs and to taking into consideration the concept that each intensity (moderate, exhaustive), duration (acute, chronic/regular), and mode/type (aerobic, resistance and the combination) of exercise training has different result and should be considered as a separate entity, we will examine the effects of inactivity, exhaustive, moderate, chronic, acute, aerobic, resistance and the combination of both types of exercise on oxidative stress in CVDs.

2.4. The Antioxidant Role of Exercise in Cardiovascular Diseases

Numerous epidemiological studies have convincingly shown that physical exercise has a beneficial effect on cardiovascular disease outcomes and it is prescribed as part of the rehabilitation in the treatment of CVDs (Alvarez et al. 2016; Sibilitz et al. 2016; Lavie et al. 2015). Furthermore, it is a well-established fact that, exercise has a lot of benefits on CVDs patientsas well as on oxidative stress. Regular exercise has a favorable effect on many of the established risk factors for cardiovascular disease, as well on enhancing antioxidant capacity.

There are numerous of reports that provide reasonable support to the notion that exercise training increases the resistance against oxidative stress, providing enhance protection (Steinbacher and Eckl, 2015). This phenomenon is not a paradox, it is a result of exercise – induced adaptations (Radak et al. 2008). Growing evidence indicates that a major benefit of exercise training is dependent on its antioxidant effects, which are mediated not only by increased expression of antioxidant enzymes but also by a reduced expression of pro-oxidant enzymes (Gao et al. 2007). ROS act as signals in exercise because decreasing their formation prevents activation of important signaling pathways that cause useful adaptations in cells. Because these signals result in an upregulation of powerful antioxidant enzymes, exercise itself can be considered an antioxidant (Gomez-Cabrera et al. 2007).

A recent study has shown that 8 weeks of aerobic exercise training, increases the total antioxidant capacity (TAC) and decreases the oxidative marker malondialdehyde (MDA) in the myocardium and ameliorates the cardiac damage induced by oxidative stress in ovariectomized rats. Improvement of oxidative stress status by exercise is associated with cystathionine-γ-lyase expression (CSE) in myocardium, suggesting that this improvement might be at least partially due to the upregulation of CSE expression (Tang Z et al. 2016).

As reviewed by Radak et al. (2008), regular exercise plays a preventive role against lifestyle-dependent diseases and the molecular mechanism behind this favorable effect could be linked to redox homeostasis, a free radical-related adaptive mechanism. The adaptive mechanism is initiated by transcription factors, resulting in increased activities of the antioxidant enzymes, and more effective repair and housekeeping by the DNA repair enzymes and proteasome complex. The molecular adaptation then leads to an improved physiological function and enhanced resistance to oxidative stress. Most importantly, the exercise-induced oxidative challenge-associated adaptation is systemic.Moreover, Camiletti-Moirón D, (2013), Mazzola PN, et al. (2011) and Radak et al. 2008, reported that regular moderate aerobic exercise appears to promote antioxidant capacity on brain.

2.4.1. *Effect of Exercise in Hypertension and Oxidative stress*

Oxidative stress has been associated with human essential hypertension (Schnackenberg, 2002, Touyz, 2000). Clinical studies demonstrated increased ROS production in hypertensive patients. These findings are basedon increased plasma levels of oxidative stress biomarkers such as oxidized protein and lipid oxidation, thiobarbituric acid-reactive substances, 8-epi-isoprostanes and on the decreased activity of antioxidants such as superoxide dismutase, glutathione peroxidase, and catalase (Moreno-Ruíz, et al. 2015, Polovina, et al. 2015, Reis, et al. 2013)**.** Excellent reviews on this topic are available (Rabattu, et al. 2015, Cohen and Tong, 2010, Touyz, 2004, Touyz, 2000). An enhanced level of antioxidant protection has been suggested recently (Larsen et al. 2016) as the mechanism underlying the decrease in ROS which, in turn, lowers blood pressure.

Exercise training has been widely recognized as an effective non – pharmacological strategy substitute for preventing and treating hypertensive patients (Jia, et al. 2014, Higashi and Yoshizumi, 2004, Zago et al. 2010). Furthermore, the beneficial effects of exercise in hypertensive subjects are thought to be mediated by an improvement of the redox status (Jia, et al. 2014, Trape, et al. 2013, Gilbert, et al. 2012). Hence, exercise training is considered as a possible therapy for decreasing oxidative stress and thereby prevent / lower and/or control high blood pressure (Larsen et al. 2016).

According to Trape et al. (2013), high level of training status leads to better results of nitrite concentration and systolic and diastolic blood pressure. Therefore, the mechanism responsible for better control of blood pressure may be associated with better antioxidant capacity achieved by higher level training status and consequently, higher nitric oxide bioavailability. Furthermore, moderate intensity exercise training has a beneficial effect in preventing the development of hypertension by lowering inflammatory cytokines, thus preventing the pathological changes to vessel cells and normalizing changes in blood pressure (Jia, et al. 2014). According to Cook et al. 2013, RT is an effective mode of exercise in modulating matrix remodeling proteins and oxidative stress, thus strengthening the role of RT in the potential prevention of the early onset of hypertension in young African American men. These findings are consistent with recent findings that, moderate aerobic training, reduces blood pressure and also provides a favorable change in antioxidant status such as malondialdehyde in plasma (Gupt et al. 2015).

As reviewed by Higashi and Yoshizumi, (2004), exercise training increases NO production and decreases NO inactivation, leading to an increase in NO bioavailability and improving

endothelial function in animal models of hypertension and in patients with essential hypertension. These findings suggest that endothelial dysfunction in hypertension is reversible. A previous study in rats has shown that, 12-weeks of low intensity aerobic exercise training, decreases oxidative stress and increases NO bioavailability, allowing a complete reversal of the augment contractile response observed in small mesenteric arteries. The results of this study demonstrate that the reduction of oxidative stress induced by exercise is responsible for the improvement in coronary artery endothelial dysfunction in hypertension (Roque et al. 2013).

In addition, ten weeks of swimming training, reduced cardiac oxidative stress, exacerbated cardiac hypertrophy, improved ventricular function, induced resting bradycardia and decreased blood pressure in spontaneously hypertensive rats (Campos, et al. 2015). These results are in agreement with a previous study in hypertensive patients, in which an intervention of a 3-weeks of low-fat, high-fiber diet combined with a low intensity aerobic exercise training, has shown great improvements in blood pressure, oxidative stress and NO availability (Roberts, et al. 2002).

These results are in accordance with previous findings from Agarwal et al. (2012), which reported that 4 weeks of moderate intensity aerobic exercise in hypertensive rats not only reduces blood pressure and improves cardiac function but also reduces inflammatory cytokines and norepinephrine, diminished activation of the nuclear factor κB (NF-κB) system, and decreased oxidative stress, as indicated by reduction in iNOS expression as well as increased levels of Cu/ZnSOD within the paraventricular nucleus (PVN).

However, Sturgeon et al. (2009), supported that changes in cholesterol levels but not oxidative stress or endothelial biomarkers were related to changes in BP variables following 6 months moderate aerobic exercise. These findings are in contrast with the results of a previous study, which suggested that the improvement of enzymatic antioxidant defense reduced mean arterial blood pressure (MABP). In that study Pialoux and colleagues (2009) reported correlations between MABP and both nitrotyrosine and 8-OHdG, specifically a 25% reduction of oxidative stress decreased MABP by 10 mm Hg.

Taken together these studies indicate that exercise training decreases blood pressure and improves endothelium-dependent vasodilation in hypertensive patients through the increased bioavailability of NO in the vascular wall.

2.4.2. *Effect of Exercise in Heart failure and Oxidative stress*

Oxidative stress has been shown to play an important role in the pathophysiology of cardiac remodeling and development of heart failure (HF) (Schuster et al. 2012; Tsutsui et al. 2011; Gao et al. 2007; Gullestad and Aukrust, 2005; Sam et al. 2005), causing cardiomyocyte death, abnormalities in transduction of myocardial β-adrenergic receptor signaling, as well as contractile dysfunction (Castro et al. 2005; Sawyer et al. 2002). According to a recent review study by Heinonen and colleagues (2015), myocardial oxygen balance is disturbed in the failing heart because of increased extravascular compressive forces and coronary microvascular dysfunction.

Additionally, there is mounting evidence that Chronic heart failure (CHF) is associated with increased oxidative stress (Gomes et al. 2015), as indicated by reduced antioxidants, a depressed oxidation reduction (redox) state and increased lipid peroxidation (Nagayoshi et al. 2009). Previous studies have shown that, oxidative stress markers such as lipid peroxides, levels of 8-hydroxy-2-deoxyguanosine (8-OHdG), a marker of oxidative DNA damage, are elevated in serum and urine of patients with heart failure, and urinary 8-OHdG reflects the clinical severity of CHF on the basis of symptomatic status and cardiac dysfunction. Results of these studies indicate that oxidative stress is involved in severity of heart failure (Kono et al. 2006; Kobayashi et al. 2011; Nagayoshi et al. 2009; Nakamura, et al. 2015).

Furthermore, activities of some antioxidant enzymes such as paraoxonase-1 (PON-1) in serum and manganese superoxide dismutase (MnSOD) in the myocardium, SOD, calatase, GPx, thioredoxin reductase, are diminished in patients with heart failure (Tang, et al. 2011, Nakamura, et al. 2015). Beyond morphological and biochemical changes, the presence of increased levels of pro-inflammatory cytokines, as well as low levels of anti-inflammatory cytokines mainly interleukin-10 (IL-10), is well document in patients of chronic heart failure (Nunes et al. 2008; Gullestad and Aukrust, 2005) associated with increased oxidative stress markers.

Extensive research has demonstrated that exercise training, reverses heart failure-associated with pathology at the clinical and molecular levels. That' s the reason why exercise training has emerged as a class I recommendation in all major national and international guidelines for the treatment of chronic heart failure (Adams & Niebauer, 2015). One of the most striking results achieved by exercise training in HF is the decrease in sympathetic nervous activity (Roveda et al. 2003, Negrao et al. 2015), associated with decreased oxidative stress,

pro-inflammatory cytokines (Gielen et al. 2003) and inducible nitric oxide synthase (iNOS) expression (Niess and Simon, 2007; Bacurau et al. 2009). According to Negrao et al. (2015), only exercise training has been shown to restore the neurohormonal balance and reverse many key features of the skeletal myopathy in patients with HF from systolic dysfunction.

Many studies have demonstrated that physical exercise is a powerful factor which improves peripheral function in chronic heart failure, both in humans and in animals. Exercise training also increases mitochondrial volume and enzyme content, improving the metabolic capacity in HF (Negrao et al. 2015). Furthermore, exercise training is well known to improve endothelial function because of an increase in shear stress that results in an increase in nitric oxide (NO) synthase (NOS) expression and activity and ultimately more bioavailable NO (Zucker et al. 2015). Koba et al. (2014), suggested that oxidative stress in the medulla in CHF mediates central command dysfunction, and that exercise training in CHF is capable of normalizing central command dysfunction through its antioxidant effects in the medulla.

Moreover, an antioxidant effect is induced by exercise training via reduction of NAD (P)H oxidase ($gp91^{phox}$, $p22^{phox}$, and Nox4) and that augmentation of the activity of radical scavenger enzymes, also benefits CHF (Adams et al. 2006; Linke et al. 2005; Gao et al. 2007). Gao et al. (2007) found that aerobic exercise training normalized sympathetic outflow and arterial baroflex function in CHF rabbits, accompanied by a regulation of SOD expression and a downregulation of $gp91^{phox}$ expression in rostral ventrolateral medulla. A recently review study by Zucker et al. (2015), suggested that exercise training reduces sympathetic outflow in heart failure state, and components of the renin ANG II system and ROS play important roles in this process in both the central nervous system and in the periphery, NO, nitric oxide.

According to Nunes et al. 2008, 8 weeks of aerobic exercise training (swimming), improves the left ventricular end-diastolic pressure and the anti-inflammatory cytokines (IL-10), reduces TBARS activity in skeletal muscle, and shows a reduction of lipid peroxidation in Wistar rats with CHF. A recent study shows that 8 weeks of aerobic exercise training, induced attenuation of cardiac endoplasmic reticulum stress in post myocardial infraction heart failure rats, by recovering cardiac proteasome activity, which related to improved left ventricular (LV) function and exercise capacity (Bozi et al. 2016). Gomes et al. (2015), have shown that, 8 weeks of low intensity exercise training, improves functional capacity of rats with aortic stenosis-induced HF regardless of changes in cardiac structures or left ventricular function, reduces oxidative stress, preserves antioxidant enzyme activity, and modulates JNK

and p-ERK expression with no changes in NADPH oxidase activity, or NF-κB pathway protein expression.

Furthermore, 8 weeks of running on a maximal lactate steady-state workload, induced structural and metabolic changes in mice with clinical sings of HF, like reduced lipid hydro peroxides, restore iNOS expression, increased activity of citrate synthase in red portion of gastrocnemius paralleled by increased capillaries per muscle fiber (Bacurau et al. 2009). A recent study has shown that 8 weeks of aerobic interval training, improved cardiac function in CHF rats, protected from the oxidative stress-induced cell death, increased the systolic Ca^{2+} transient amplitude and improved diastolic Ca^{2+} removal in CHF (Kraljevic et al. 2015)

In a human study, 8 weeks of unsupervised, home-based exercise training, leads to significant improvement in physical work capacity and leads to a normalization of hypoxanthine levels (a pro-oxidant substrate and a marker of hypoxia) in patients with stable CHF (Ni**e**bauer et al. 2005). In addition, Tsarouhas et al. (2011), demonstrated that moderate, unsupervised, everyday physical activity was able to ameliorate the lipid and glycemic profile of CHF patients, with simultaneous attenuation of inflammation and oxidative stress. Furthermore, in CHF patients, 6 months of regular aerobic exercise training, resulted in an increased in Cat and GPX activity in skeletal muscle, by 42% and 41% respectively and decreased in Lipid peroxidation by 57%. However, despite the augmentation in Cat and GPX levels, exercise training failed to affect total SOD activity, suggesting a persistent impairment of superoxide radical detoxification in the skeletal muscle (Linke et al. 2005). These results lead to the conclusion that exercise training by restoring skeletal muscle mass, metabolism, redox state, and muscular phenotype can be considered an important therapeutic strategy for preventing or reversing skeletal muscle myopathy in HF.

2.4.3. *Effect of Exercise in Atherosclerosis and Oxidative stress*

Atherosclerosis is a chronic inflammatory disease of vessels which is known to be associated with blood lipids disorder, mitochondrial DNA damage (Fetterman et al. 2016) and oxidative stress. Accumulating evidence suggests that endothelial dysfunction is an early marker for atherosclerosis (Li et al. 2014). Dysfunction of the endothelial lining of lesion-prone areas of the arterial vasculature is an important contributor to the pathobiology of atherosclerotic cardiovascular disease (Gimbrone and García-Cardeña, 2016).

In addition, the enhancement of lipid peroxidation or the decrease of antioxidant protection present in metabolic diseases or bad lifestyle can induce endothelial dysfunction

and atherosclerosis (Lubrano and Balzan, 2015). According with Davignon and Ganz (2004), a defect in the production or activity of nitric oxide leads to endothelial dysfunction, signaled by impaired endothelium-dependent vasodilation. Nitric oxide opposes the effects of endothelium-derived vasoconstrictors and inhibits oxidation of low-density lipoprotein. Clinical studies have shown that oxidative stress can increase ROS reducing the formation of antioxidant defense, especially in subjects with coronary artery disease (CAD) (Lubrano and Balzan, 2015) and the formation of ROS is critical event in the development of atherosclerosis (Nagayoshi et al. 2009). The control of oxidant status and metabolism of lipoproteins in the body has become an important tool for combating atherosclerosis (Teodoro et al. 2012).

Different types and modes of exercise training, have beneficial effects on the regression of subclinical atherosclerosis (Pellegrin et al. 2015; Beck et al. 2013). Regular physical exercise not only improves clinical symptoms, but it also effects the progression of atherosclerosis, stabilizes, and reduces rupture of atherosclerotic plaque, improves endothelial – dependent relaxation, which is protective against eNOS-NO dysfunction in atherosclerosis (Shing et al. 2015; Pellegrin et al. 2015; 2014; Li et al. 2014; Kadoglou et al. 2013; Okabe et al. 2007; Laufs et al. 2005). These effects are at least partially due to improved endothelial dysfunction through increased NO bioavailability (Walter et al. 2004).

In addition, recent data showed that, following 12 weeks of voluntary wheel running training, reduced atherosclerotic plaque area, increased cytokines in apolipoprotein E Knockout ($apoE^{-/-}$) mice (Shing et al. 2015). According to Kadoglou and coworkers (2013), 6 weeks of treadmill training in diabetic $apoE^{-/-}$ mice, can stabilize vulnerable atherosclerotic plaques through the modulation of inflammatory pathways and MMPs. Moreover, 4 weeks of treadmill training in low lipoprotein receptor knockout ($LDLr^{-/-}$) mice, reduced atherosclerotic plaque formation. These changes may have resulted from modulation of lipid metabolism, possibly by stimulating cholesterol reverse transport lipoprotein genes and through a set of anti-inflammatory cytokine genes (Garelnabi et al. 2014). These results are in agreement with a previous study, reporting that swimming training (8 weeks) reduced atherosclerosis by antioxidant effects via the vascular NO system in apolipoprotein E deficient mice (Okabe et al. 2007).

Furthermore, some researchers have examined the effects of combined exercise and diet on lipid profile, inflammation and atherosclerosis (Cesar et al. 2010) and their association with oxidative stress (Lee et al. 2014). According to Lee et al. (2014), combination of swimming

training (8 weeks) and diet supplementation decreased of the oxidative stress by reducing 4-HNE, enhanced aorta vasodilatation by increased NO and eNOS expression in aorta, decreased of CRP and pro-inflammation proteins in aging model rats with diet-induced atherosclerosis.

In previous studies, it was suggested that increased antioxidant enzymes may reduce atherosclerosis through the co-activation of vascular relaxation mediated by nitric oxide (NO) as the radical O2 dismutation increases the bioavailability of NO in endothelial cells; in the presence of the O2 radical, NO shifts to formation of peroxide nitrite (Lubrano and Balzan, 2015; Yang et al. 2009; Lewis et al. 2007). Furthermore, according with Teodoro et al. (2012), moderate and low intensity aerobic training (30 min daily for 8 weeks), increased antioxidant enzymes activity (SOD and GPx), caused reduction of lipid hydroperoxides and protein carbonyl content and decreased atherosclerotic lesions in mouse models of atherosclerosis.

2.5. Aerobic exercise training and oxidative stress

It has been reported that pathways which attenuate mitochondrial oxidative stress, regulate mitochondrial biogenesis, and/or improve mitochondrial function, emerged as potential therapeutic targets for the amelioration of vascular dysfunction and prevention of the development of age-related vascular diseases (Vendrov AE et al. 2015,Ungvari Z, et al. 2010).

According to Chen et al. (2011), protection of the mitochondria from bioenergetics failure and oxidative stress resulting in apoptosis in the ischemic tissue, may open a new vista to the development of more effective neuroprotective strategies against ischemia-induced brain damage. Furthermore, a previous study (Maulik et al. 1995), suggested that a controlled amount of oxidative stress induces the expression of intracellular antioxidants that can result in enhanced myocardial tolerance to ischemia. This suggests that myocardial adaptation to oxidative stress may be a potential tool for reduction of ischemic/reperfusion injury.

Hypothetically, the greater rate of flow of electrons through the mitochondrial electron transport chain caused by increased oxygen consumption during aerobic exercise, could amplify free radical production. During the resting state, the human body, produces reactive oxygen species (ROS), but at such levels within the capacity of the body's antioxidant defense system (Mastaloudis et al. 2001). Because aerobic exercise training induces higher oxygen consumption and in parallel with increased ROS production (Powers SK, et al. 2008), an antioxidant system is launched during such training, so as to maintain an adequate redox

balance (Smuder, et al. 2011). In addition, aerobic exercise, improves mitochondrial function and even increases the number of muscle mitochondria (Boveris & Navarro, 2008; Ljubicic et al, 2009).Furthermore, it enhances the adaptation to oxidative stress by increasing level of antioxidants (Larsen et al. 2016). Therefore, aerobic exercise, increased ROS production as well as up-regulation of antioxidant enzyme activity and expression. The net effects of training improve efficiency of the antioxidant defenses and oxygen consumption (Smuder, et al. 2011; Kaczor et al. 2007). However, the chronic effects of exercise training differ from acute effects of exercise and therefore these exercise modes should be considered as separate.

2.5.1 *Acute aerobic exercise*

On the other hand, according to Taylor et al. (2014), repeated bouts of sustained and/or high intensity aerobic exercise, such as that required for marathon training and competition, evokes systemic vascular remodeling that shifts the effect of aerobic exercise from cardio-protective to atherogenic. Furthermore, Mastaloudis et al. (2001) have shown that extreme endurance exercise results in the generation of lipid peroxidation with concomitant increase in vitamin E disappearance.

In addition, Kliszczewicz et al. (2015), suggested that the oxidative stress response is proportional to the exercise intensity performed. In that study, following an acute bout (90% of HRmax) of exercise, plasma lipid hydroperoxides (LOOH) and ferric-reducing antioxidant power (FRAP) were increased immediately post exercise and remained elevated 1-h and 2-h post exercise, whereas protein carbonyls (PC) and trolox-equivalent antioxidant capacity (TEAC) were decreased immediately post exercise and remained low 1-h and 2-h post exercise, in healthy individuals. Moreover, Francescato et al. (2014), showed that a single bout of prolonged moderate intensity aerobic exercise (3-h walk at 30% of heart rate reserve) did not increase the lipid peroxidation levels, whereas an increase in the antioxidant defense was observed at the end of the exercise.

In contrast, according to Brito et al. (2015; 2015), exercise intensity promoted lipid peroxidation in the heart, aorta, lung and trachea in Wistar rats. In these studies, low intensity swimming exercise promoted acute vasorelaxant activity and increased lipid peroxidation, however high intensity swimming exercise (above the anaerobic threshold), reduced the relaxant effect of exercise and led to further increased in lipid peroxidation.

However, according to Bouzid et al. (2014), regular low intensity aerobic exercise, may be useful to prevent acute exhaustive aerobic exercise-induced oxidative stress by upregulating some antioxidant enzyme activities. In addition, Seifi-skishahr and colleagues (2016) supported that,the effect of high intensity acute exercise on glutathione redox ratio, depends on physical training status of individuals and it seems that a lifestyle with moderate regular exercise training, will improve health by shifting in "redox" balance towards more reducing environment, encountering stressful conditions. In that study, the authors have shown that physical training status affected the plasma GSH/GSSG and Cys/CySS ratio and red blood cells GSH/GSSG ratio at baseline and after exercise.

2.5.2 *Chronic/regular aerobic exercise*

In a recent study, Zembron-Lancy et al. (2016) have shown that, there is a positive correlation between VO2max and total antioxidant status (TAS). In addition, according to Kaczor et al. (2007), in the first few weeks of low intensity exercise, ROS generation increases and markers of oxidative stress are elevated. However, adaptation occurs over the duration of training, resulting in a lower generation of free radicals in mice. Therefore, aerobic exercise training enhances the antioxidant defenses in various tissues, particularly in the skeletal and cardiac muscles. Furthermore, according toClaudio et al. 2013, swimming training, may play an important role in coronary vascular reactivity and in the expression of antioxidant enzymes, which may be one of the reasons why exercise reduces the risk of coronary heart disease in postmenopausal women. In addition, Chis and colleagues (2015), have shown that following a 4 weeks programme of moderate aerobic exercise training (swimming), improved hyperglycemia, hypertriglyceridemia, hypercholesterolemia and antioxidant status as shown by the increased in SOD and CAT and the decreased in MDA, PC, NOx and iNOx levels in aortic tissue in Wistar diabetic rats.

Previous study suggested that, aerobic training increased tolerance to exercise-induced oxidative stress in overweight/obese adolescent girls partly as a result of improved body composition. More specifically, Youssef et al. (2015), a 3-month multivariate aerobic training programme prevented exercise-induced lipid peroxidation and/or inflammation in overweight/obese girls.

Coelho et al. (2013) demonstrated that, aerobic exercise training was able to prevent atrophy, oxidative stress and muscle damage in skeletal muscle in a rat sepsis model. The exercise which causes an increase in the antioxidant defense system of muscles is most likely the underlying mechanism responsible for protecting muscle cells against oxidative damage

(Coelho et al. 2013). According to Naderi et al. (2015), 6 weeks of voluntary moderate aerobic exercise training, has shown positive changes in MDA, SOD, GPx and CAT activities in the heart tissue of Wistar rats. These findings indicate that, voluntary exercise, is a proper method for the protection of the heart. Furthermore, 8 weeks of moderate aerobic exercise (swimming) can diminish heart expression of lectin-like low density lipoprotein (LOX-1) receptor in accompany with reduction of oxidative stress without any lipid profile alterations in high fat diet rats (Riahi et al. 2015). In addition, data in a recent study (Alghadir et al. 2016), has shown that 24 weeks of a moderate aerobic exercise training, modulated redox and inflammatory status of healthy older adults . Specifically, according to Alghadir and colleagues (Alghadir et al. 2016), there was significant increase in the activity of TAC and decrease in the levels of MDA, 8-OHdG, and hs-CRP in participants of exercise group following 24 weeks of moderate aerobic training.

In contrast, previous study demonstrated that, short period of aerobic exercise training (8 weeks) failed to cause any rest adaptation in oxidative stress markers. Specifically, Kelly et al. 2007, reported that 8 weeks of aerobic exercise training cannot change adipokines (C-reactive protein, interleukin 6, tumor necrosis factor alpha, adiponectin, leptin, and resistin), and oxidative stress markers (8-isoprostane) in overweight children.

However, a recent study observed that low intensity aerobic exercise training (9 weeks) prevented an increase in myocardial lipid peroxidation and attenuated a decrease in antioxidant enzymes activity in type 1 diabetes rats (Gimenes et al. 2015). In addition, Holland et al. (2015), supported that 10 days of moderate intensity treadmill training in rats, up-regulates key endogenous antioxidant enzymes and decreases inflammation markers in ileum tissue 24h post exercise. Moreover, Hoffman-Goetz et al. (2009), found a similar response after 16 weeks of moderate endurance exercise, with a significant increase of SOD1 and catalase in intestinal lymphocytes.

Furthermore, 16 weeks of intense aerobic exercise training (80-85% HRmax), decreased systemic oxidative stress as measure by F2-isoprostanes only in sedentary young women with the highest quartile of plasma F2-isoprostanes at baseline (Arikawa et al. 2013). Vinetti et al. (2015), have shown that 12 of months supervised moderate aerobic, resistance and flexibility training (total 140-270 min/ week, gradually increased), can affect positively insulin sensitivity and blood levels of LDL cholesterol, increase cardiorespiratory fitness, and plays a role in the amelioration of oxidative stress status in type 2 diabetes mellitus, as revealed by

the reduced of plasmatic oxidation products of phospholipid 1-palmitoy-2-arachidonyl-sn-glycero-3phosphorylcholine (oxPAPC).

2.6. Resistance exercise and Oxidative stress

Resistance exercise (RE), can have multiple health benefits to individuals, especially those experiencing diminished muscle mass and function (Gordon et al. 2011). Pertaining literature reports that resistance training has a favorable effects on many of the established risk factors for cardiovascular diseases, such as hypertension, diabetes mellitus, obesity, increased plasma lipids and endothelial dysfunction. Furthermore, several studies have indicated that resistance training in cardiovascular disease patients, is safe since it causes favorable physiologicaladaptations (Volaklis et al. 2015, Ghilarducci et al. 1989; Kelemen et al. 1986; McCartney et al. 1991; Sparling et al. 1990; Williams et al. 2007).

Despite numerous studies investigating the effects of aerobic exercise on oxidative stress and inflammatory reactions in CVD related risk factors, few researchers have investigated the effects of resistance exercise on redox status and the inflammatory response in CVD patients. It has been reported that an acute bout of unaccustomed RE, can illicit inflammation in skeletal muscle; however, long term RE training is associated with inti-inflammatory benefits (Calle and Fernandez, 2010).

2.6.1. *Acute resistance exercise*

A recent study has shown that an acute resistance exercise performed at low to moderate intensity (50-75% of 1 RM) inlow risk patients with coronary artery disease, is safe and does not exacerbate the inflammation associated with their disease (Volaklis et al. 2015). Esgalhado et al. (2015), suggested that acute intradialytic strength exercise (60% of 1-RM) was unable to reduce oxidative stress damage and inflammation in chronic kidney disease patients undergoing hemodialysis. Additionally, this exercise seems to reduce plasma SOD levels, which could exacerbate the oxidative stress in these patients.

According to Gomes et al. (2016), a single bout of high intensity interval training, promotes lymphocyte oxidative stress and reduces lymphocyte proliferation in response to super-antigenic stimulation. Furthermore, Ramel et al. (2004) reported that, following an acute RT (9X10~75% of 1RM) in healthy men, increases lipid oxidation products and antioxidant concentrations.

In contrast, the results of Mcanulty et al. (2005) indicated that exhaustive resistance exercise, did not result in increased oxidative stress as measures by F2-isoprostanes.

Furthermore, Deminice et al. (2010) reported that an acute session of RE, induces oxidative stress in plasma of trained men after acute resistance training, which was not found in saliva samples except for uric acid. This is in disagreement with previous investigations involving RE, indicating that high intensity resistance exercise induces oxidative stress, systemic in inflammation, and cellular damage indices in athletes (Atashak et al. 2013). Moreover, Cardoso et al. (2012) showed that an acute RE, in elderly women, increases oxidative stress markers but decreases antioxidant defense, immediately after the exercise. The results of a previous study, showed that superoxide dismutase activity in response to acute exercise, was significantly higher in young compared to older adults. These data suggested that signal transduction of acute exercise may be impaired with aging (Nordin TC et al. 2014).

2.6.2. *Chronic resistance exercise*

Chronic RE has proved to have an important therapeutic potential role, by promoting skeletal muscle mass gain, increased insulin sensitivity and blood glucose reduction (Marcelo Mendonça Mota et al. 2014). Moreover, it has been reported that RT contributes to prevent/treat pathologies that affect the metabolism and cardiovascular function. Li and colleagues (2015), found that following 12 weeks of a progressive resistance exercise protocol, phosphorylation of AKT and eNOS as well as expression of redox factor 1 and MnSOD were significantly increased while FOXO1 phosphorylation decreased in rat aorta. These results, provide evidence that RT can improve the function of the aorta and protect the balance of oxidative stress and antioxidant function.

Furthermore, Gordon et al. (2011), suggested that with 12wks of RE training in healthy men and women, the transient transcriptional downregulation of mitochondrial structure and oxidative phosphorylation, as well as glucose metabolism is suppressed in skeletal muscle.

According to Tarnopolsky (2009), resistance exercise training, is an effective countermeasure for aging-associated muscle atrophy, and is associated with less oxidative stress and increase of mitochondrial capacity.

In a previous study, Vincent et al. (2006) have shown that six months of RE training, reduced systemic oxidative stress levels and homocysteine in overweight/obese and normal-weight elderly adults, however this exercise programme, did not induce significant changes in total cholesterol, HDL-C, and Lp(a).

According to Camiletti-Moiron et al. (2015), catalase activity levels, increased after 12 weeks of high intensity resistance training protocol in motorized treadmill, however did not alter

the other antioxidant enzymes such as manganese superoxide dismutase (Mn-SoD) and cooper/zinc superoxide dismutase (CuZn-SOD) brain activity in rats.

Furthermore, Cakir-Atabek H et al. (2010) suggested that, chronic RE has protective effects against oxidativestress similar to aerobic exercises and that these effects seem to be independent of the training intensity. In addition, resistance exercises performed at very low intensity (30-40% of 1 RM), may fail to develop adaptation up-regulation in the antioxidant defense system (Cakir-Atabek et al. 2015). In contrast, 12 weeks of high intensity resistance exercise with progressive increases in both training intensity and volume, did not change blood lipids, total cholesterol, high-density lipoprotein, LDL, triglycerides and oxLDL (Croymans et al. 2014).

Carteri et al. (2015) supported that resistance exercise protocols composed of a single set of seven exercises, regardless of the intensity or total workload, do not induce to oxidative stress, suggesting that volume is the main variable to induce oxidative stress in resistance trained men. This opinion is in agreement with the results of a recent study, which has shown that 12 weeks of low volume RT (7 exercises X8-12reps) did not increase in vitro skeletal muscle oxidative capacity or reduce mitochondria ROS production in healthy older males (Flack et al. 2016).

Ghiasi et al. (2015), suggested that adaptation and alteration in oxidative stress and cell injury level in heart, depend on duration of exercise and may be due to reducing of the basic deteriorative reactions produced by lipid peroxidation. In that study, the authors have shown that in heart tissue samples, GPX activity significantly increased and level of MDA appears to be significant lower in heart of rats which performed 16 weeks of RT, in comparison to rats which performed 4 weeks of RT.

According to Cardoso et al. (2012), resistance trained women show improved antioxidant capacity and lower oxidative damage than sedentary ones. Moreover, 12wks of low intensity of RE training, leads to a high abundance of antioxidant enzymes and lower oxidative stress in elderly men (Parise et al. 2005). This is in agreement with previous investigations involving RE, indicating that that 6-month RE training programme reduces exercise induced oxidative stress and homocysteine regardless of adiposity, indicating that protection can be afforded in an older, overweight/obese population effectively as in healthy older adults (Vincent HK et al 2006).

Although it is generally accepted that chronic RE improved antioxidant status, a single acute bout of RE appears to promote oxidative stress and antioxidant capacity as indicated in some, but not all, studies.

2.7. Combination of aerobic and resistance training and oxidative stress

Resistance exercise (RE) is characterized by the use of energy above critical power and is supplied via the anaerobic metabolism, which results in high accumulation of lactic acid (Cardoso et al. 2012). During aerobic exercise, the intensity of forces are generated, while repetitive is low. On the contrary, RE is characterized by high force, but far lower volume, contractions that are associated with much lower O2 flux. Hence, the mechanism by which high force contractions generated free radicals is generate though to occur post exercise and is associated with inflammatory cells invading damage muscle (Victor R. Preedy, Ronald Ross Watson, CABI, 2007 - Medical - page: 564).

These two types of training programs have been widely investigated. Their combination has recently been recommended for health purposes in a wide of variety populations (De Souzaet al. 2014). Nevertheless, the effect of the combination of aerobic and resistance exercise on oxidative stress has been minimally studied. It is supported that there are no differences between aerobic and resistance exercises regarding oxidative stress parameters (Cardoso et al. 2012; Cakir-Atabek H et al. 2010; Bloomer RJ et al. 2005). This is in agreement with previous investigations, indicating that endurance training, resistance training and the combination of them induced the same changes on circulating antioxidant capacity and oxidative stress (Azizbeigi, et al. 2014). Recent evidences have also shown that DNA damage and oxidative DNA damage decreased, while physical fitness and total antioxidant capacity increased in healthy men, after 16 weeks of combined physical exercise training (Soares et al. 2015).

2.8. Exhaustive – Strenuous Exercise and Oxidative stress

It is widely described that chronic exercise, reduces oxidative stress and damage, both by decreasing ROS production and increasing antioxidant capacity, and improves mitochondria efficiency in several organs and systems. Furthermore, after an exercise training program, a reduction of DNA damage resulting from increase in both repair and antioxidant capacity, is also expected.

As we have already mentioned, there is increasing evidence that ROS not only are toxic but also play an important role in cell signaling and in the regulation of gene expression. Moreover, it has been reported that regular low intensity exercise, decreases oxidative

stress and encompasses increase antioxidant defenses. It also, reduces basal production of oxidants, and diminishes radical leak during oxidative phosphorylation (Napoli C et al. 2006; Leeuwenburgh C, Heinecke JW, 2001).

Moreover, although most of the studies reviewed here (Table 2&3) found that moderate aerobic exercise, resistance or a combined exercise training had beneficial effects on oxidative stress markers, conflicting results have also been shown. After an exercise programme, oxidative stress markers were found to be decreased (Silva et al. 2017), increased (Fatouros et al. 2010; Nikolaidis, et al. 2007; Aoi et al. 2004), or remained unchanged (Venojärvi M et al 2013). The variability in animals or humans characteristics, their training status, basal level of antioxidant capacity, type of diet, the variation in timing of tissues sampling, the differences in exercise intensity and duration, as well as the methodological limitations, can account for some of the conflicting results between studies.

Despite the many known health benefits of exercise, there is a body of evidence suggesting that exercise causes oxidative stress. As it is widely known, exercise induces a multitude of physiological and biochemical changes in blood. Moreover, blood interacts with all organs and tissues and, consequently, with many sources of reactive species. Plasma and blood cells can autonomously produce significant amounts of reactive species at rest and during exercise that may affect its redox status (Nikolaidis and Jamurtas, 2009). However, do all kind of exercises and intensity, cause oxidative stress? The answer to this is likely to be no.

Most of the researchers suggest that exercise increases ROS, and causes oxidative stress only when exhaustive. That's the reason we have to separate regular-moderate and strenuous – high intensity exercise, and the type/mode of exercise performed (aerobic and resistance exercise). According to Camiletti-Moirón D (2013), anaerobic or high-intensity exercise, aerobic-exhausted exercise, or the combination of both types of training, could deteriorate the antioxidant response.

Strenuous exercise increases free radical in skeletal muscle (Davies et. al. 1982), causes oxidation of gloutathione, realeases cytosolic enzymes and other sings of cell damage. A number of studies have shown that high intensity exercise, increases the production of ROS, and the sources of oxidative stress are inflammatory responses mediated by neutrophils, the release of transition metals, the interaction of methemoglobin with lipid peroxides and the activity of xanthine oxidase (Parker et al. 2008). According to Gomez-Cabrera et al. (2007) xanthine oxidase is involved in the generation of superoxide associated with exhaustive exercise.

Popovic et al. (2012) suggest that exercise to exhaustion induces the generation of oxidative stress predominantly by oxidative modification of protein molecules. All these findings can be shown by the increasing biochemical indices of oxidative stress measured either systemically or in the working muscle after strenuous exercise (Reid, 2007). As reviewed by Reid (2008), Sen (1995) and Alessio (1993) exercise promotes glutathione oxidation and depletion of total glutathione. Increases are also detected in markers of lipid peroxidation (Mastaloudis et al. 2001), protein carbonylation (Garten, R. S. et al. 2015), nitrotyrosine adducts (Bailey DM, et al. 2011; Barreiro E et al. 2009), and DNA oxidation (Tsakiris et al. 2006; Ogonovszky et al. 2005; Orhan et al. 2004).

Furthermore, Aoi et al. (2004) and Sugama et al. (2015), suggested that muscle damage after prolonged exercise, is related to inflammation secondary to phagocyte infiltration caused by ROS. Recently, Sugama et al. (2015), examined systemic oxidative stress and inflammation induced by endurance race within two groups (damaged group and minor-damage group). In the damaged group, the authors found inflammatory markers, serum concentrations of diacron reactive oxygen metabolites (d-ROMs) as an oxidative stress marker, but also anti-inflammatory markers, biological antioxidant potential (BAP) and total antioxidant capacity (OXY), as antioxidant capacities tend to be higher than those in the minor-damage group immediately after the race.

In addition, Jorde et al. (2007), have shown that after maximal exercise, an increase of oxidized low – density lipoprotein (oxLDL) in CHF patients has occured but not in the healthy control group. However, a recently cited study by Goff et al. (2014) reported that, following a maximal isokinetic eccentric exercise, although the increase of oxidative stress biomarkers was no release of cardiac biomarkers. Furthermore, Goff et al. concluded that this kind of strenuous exercise may be performed without any risk to the patient's heart.

2.9. Detraining, cardiovascular disease, and oxidative stress

Detraining is the partial or complete loss of training-induced adaptations, in response to an insufficient training stimulus (Mujika, Padilla, 2000). According to Toraman and Ayceman, (2004), the detraining effects differ according to the age in elderly people. Among all age groups, CVD patients have higher possibility for training disruptions due to plan or unplanned factors, ranging from illnesses to vacations.

Although the fact that exercise training is very important for cardiovascular diseases and oxidative stress, the detraining effect in terms of how long the effect of exercise training lasts for these parameters, is equally important. It has been reported that detraining has

negative effects on cardiovascular adaptations (Kemi et al. 2004). The question is: Is the type/mode and the intensity of exercise, or the duration of exercise training protocol that affects the detraining effect?

2.9.1. *Detraining and resistance exercise Detraining and resistance exercise*

Miyachi et al. (2004) have shown that the exercise improvements in left ventricular (LV) wall thickness, LV mass index, LV hypertrophy index and arterial compliance values, returned to the baseline values after 4 months of detraining preceded by 4 months of high load resistance training (80% of 1RM). Therefore it appears that, 4 months may lead to a complete reversal of the cardio-protection offered by exercise training.

On the other hand, previous studies have shown that muscular strength of elderly individuals, when subjected to resistance training of moderate to high intensity, can be maintained above baseline levels during 2 to 52 weeks of detraining (Esain et al. 2017; Coetsee and Terblanche 2015; Yasuda et al. 2015; Harris et al. 2007; Fatouros et al. 2005, Taraman 2005). According to Harris et al. (2007), despite the strength losses, significant levels of total-body strength were retained even after 20 weeks of detraining following an 18 weeks progressive resistance training.

These results are also in line with previous research. Despite a significant decrease in muscle strength/size after 12 weeks of detraining period, following an 12 week home based moderate resistance training using low-load elastic band (with blood flow-restricted), Yasuda et al. (2015) reported that their participant's (older women) muscle strength/size was still significantly higher compared to baseline values.

The same trend was described by Coetsee and Terblanche (2015), where gains in muscle strength and submaximal endurance capacity were not completely lost after 16 weeks of detraining following a 16 week progressive resistance training programme in older individuals.

Furthermore, Fatouros et al. (2005), have shown that 24 weeks of high intensity resistance training induced greater gains in strength, anaerobic power, and functional capacity than 24 weeks of low resistance training in elderly individuals. Moreover, after 48 weeks of detraining, the high intensity resistance training protocol was shown to be more effective at maintaining of these beneficial effects than aerobic training protocol. Therefore, it appears that exercising at a higher intensity, results in a lower rate of strength loss during detraining, and strength gains are maintained for a longer period of time.

According to Stebbins et al. (2013), 8 weeks of progressive lower limb resistance training (80% of 1-RM), increased muscular strength, decreased resting heart rate, increased superficial femoral artery (SFA) and carotid artery (CA) diameters and mean blood flow. However, after a detraining period (2-4 weeks), a reversal of these training changes occurred, with reductions to below baseline levels apparent in SFA diameter and CA blood flow. Most of these changes occurred within the first 2 weeks of the detraining period, suggesting that both resting arterial diameter and blood flow changes, occur rapidly once exercise training ends. It is therefore evident that exercise and inactivity affect the human vasculature.

In contrast, according to Nascimento et al. (2014) after 14-weeks detraining period, following 14-weeks resistance training at a moderate intensity, hypertensive older women were able to maintain the benefits on blood pressure and muscular strength.

2.9.2. *Detraining and aerobic exercise*

Recent approaches to exercise detraining and adipose tissue in rats have pointed out that physical detraining might play a role as a possible obesogenic factor for increasing glucose uptake and oxidation (Sertie et al. 2015; 2013; Mazzucatto et al. 2014).

In a previous study, 8 weeks of moderate aerobic training reduced the adipocyte size while physical detraining caused adipocyte hypertrophy in rats. Specifically, 4 weeks of physical detraining, accelerated their weight gain rate and completely recovered it, reaching the sedentary group, allowed total adiposity recovery by increasing the lipogenic capacity relative to training group (Sertie et al. 2013). Additionally, according to Sertie and colleagues (2013), physical detraining may have stimulated the adipogenic process and attenuated apoptotic events which may contribute to a rapidly recover of the adipose mass.

In a recent study by Sertie et al. (2015), physical training (8-weeks, moderate aerobic exercise) interruption, did not cause an immediate loss of the acquired adaptations. In that study, during a 4-week detraining period, the adipocytes from detrained rats were more responsive to insulin and more effective in taking up glucose when stimulated with insulin compared to those from the sedentary group. From these results the authors hypothesized that, owing to the more intense glucose entrance into adipose cells from detrained rats, more substrate became available for triacylglycerol synthesis. Furthermore, this increased glucose oxidation rate allowed an increase in energy supply for triacylglycerol synthesis.

According to Waring and colleagues (2015), following 4 weeks of detraining, the anatomical and functional adaptations gained through 4 weeks of intensity-controlled aerobic exercise training (80-85% VO2max), are lost in male rats. According to Maeda et al. (2001), the increase in nitric oxide level (vasodilator substance) and the decrease in endothelin-1 level (vasoconstrictor peptide) in healthy individuals, lasted to the 4th week after the cessation of a moderate aerobic exercise training (8-weeks) and these levels returned to the pre-exercise levels in the 8th week after the cessation of exercise training.

Furthermore, Koshiba and Maeshima (2015), reported that the diastolic pressure and the changes in arterial stiffness are maintained after a detraining period of 6 and 3 months respectively in endurance athletes.

These findings are in agreement with the results of a previous study (Spence et al. 2011), showing that 6 months of intensive aerobic exercise training (progressive) in young, untrained subjects lead to increased aerobic fitness, left ventricular (LV) mass, left ventricular end-diastolic volume (LVEDV), and interventricular wall thickness, whereas no changes observed in these parameters in resistance training (65-85% of 1-RM) group. Furthermore, after 6 weeks of detraining all changes had returned to baseline values except LVEDV which remained elevated.

In addition, Kemi et al. (2004) found similar results in rats following 2-4 weeks of detraining. In that study, 8-10 weeks high intensity aerobic exercise training, increased VO2max, improved myocardial and endothelial responses. Whereas training induced Vo2max and myocardial effects regress over 3 to 4 weeks of detraining, exercise-gained endothelium dependent relaxation is completely abolished within 2 weeks of detraining.

Taraman (2005), reported that six weeks of detraining did not reverse the gains in aerobic endurance and agility made during a nine week exercise programme in young-old (aged 60–73 years) adults and the gains in lower body strength of young-old and old (aged 74–86 years) elderly people. However, prolonged detraining (52 weeks) caused a loss of all gains made during the nine week training programme and caused a dramatic decrease in aerobic endurance in subjects of 74 years of age and older.

Furthermore, it has been reported that 2 weeks of detraining reduced VO2 max in Wistar rats by 22% compared, indicating loss of aerobic capacity reversed the resting heart rate near baseline values, following 10 weeks of moderate aerobic training programme (Evangelista et al. 2005).

2.9.3. *Detraining and combined exercise*

Furthermore, an 8-month of moderate intensity training programme combining aerobic and resistance exercise, induces favorable muscular and biochemical adaptations, on total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), apolipoproteins A1 (apo-A1) levels, protecting patients with coronary artery disease, which, after 3 months of detraining, the favorable adaptations were reversed (Tokmakidis and Volaklis , 2003). These results are in contrast with a recent study in our lab (Theodorou et al. 2016), where participants completed detraining tests over a period of 1 to 3 months following a 8 month moderate training programme (aerobic, resistance, combine). In that study, individuals with coronary artery disease followed an 8 months of moderate exercise training (aerobic, resistance, combine) and after 3 months of detraining, muscle strength was still significantly higher compared to the baseline values in both resistance and combine exercise training groups but not for the aerobic training group. The same results occurred in the blood lipid profile (TC, TG, HDL-C, LDLC) which were still significantly lower compared to the baseline values at the second month of detraining period, for the aerobic and combined exercise training groups but not for the resistance training group. Furthermore, all groups revealed favorable alterations in hs C-reactive protein (CRP) until the 1st month of detraining period.

In addition, Farias et al. (2015) have shown that both moderate aerobic and resistance training protocols (6 weeks) are able to improve lipid profile glycaemia in a fasted state and the level of HbA1C in a group of non-medicated individuals with DMII. However, after 6 weeks of detraining, the resistance protocol was shown to be more effective at maintaining the effects attained on HDL-C, LDL-C and HbA_{1C} than the aerobic training protocol.

2.9.4. *Detraining and oxidative stress*

Recent approaches to exercise and inflammation in CVDs, have pointed out that after myocardial infraction in rats, moderate aerobic exercise training (2 months) was able to improve autonomic modulation to the heart and vessels. In addition, the cardiovascular autonomic modulation improvement by exercise training was correlated with reduced inflammatory cytokines on the heart and adipose tissue. Furthermore, these benefits were sustained even after one month of detraining. Although, no expressive changes were observed in oxidative stress and lipolytic pathway with exercise training and detraining (Rodrigues et al. 2014).

Moreover, according to Agarwal and colleagues (2012), 2 weeks of detraining preceded by 4 weeks of moderate intensity aerobic exercise in AngII-induced hypertensive rats, abolished the exercise-induced attenuation in oxidative stress within the paraventricular nucleus (PVN), as indicated by increased levels of iNOS as well as reduction in Cu/ZnSOD after detraining. In addition, detraining did not have any detrimental effects on exercise induced improvement in pro-inflammatory cytokines (PICs), whereas, it abolished the exercise induced improvement in IL-10 in the PVN of hypertensive rats. However, two weeks of detraining did not abolish the exercise-induced attenuation in MAP in hypertensive rats, whereas, detraining failed to completely preserve the exercise-mediated improvement in cardiac hypertrophy and diastolic function in these rats.

All these findings reflect the long lasting effects of exercise training and suggest that even if individuals cannot train for a period of time, all is not lost.

2.10. Physical inactivity and Oxidative stress in Cardiovascular Diseases

It has been proposed that, physical inactivity leads to impairment in physiological functions and reduces the whole body resistance to oxidative stress (Samjoo et al. 2013). Measurements of oxidative stress are significantly higher in sedentary versus active adults (Bouzid MA et al. 2014; Bartfay W, Bartfay E, 2014). According to Radak et al. (2011), has shown that the levels of 8-Oxoguanine (8-oxoG) in old inactive subjects were higher compared to old active subjects, indicating that regular exercise induces an adaptive response that involves an improved, more efficient antioxidant and DNA repair machinery.

In addition, it seems that physical inactivity through molecular pathways could facilitate the incidence of oxidative stress-related diseases (Radak et al. 2008, Bartfay W, Bartfay E, 2014).

According to Pialoux et al. (2009) physical inactivity has a positive association with oxidative stress and cardiovascular risk factor such as blood pressure, BMI, %body fat etc. in postmenopausal women. Furthermore, in a previous study in mice, physical inactivity increases vascular oxidative stress, ROS production, as well as protein expression of the NADPH oxidase subunits p47phox and p67phox, in the endothelium and the media of the aortic wall, develops atherosclerotic lesions in the aortic root and ascending aorta, impairs endothelium-dependent vasorelaxation of inactive mice as opposed to active animals (Laufs et al. 2005).

Moreover, in a recent study, Park and Kwak (2016), have shown that although there was no difference in resting oxidative stress and antioxidant capacity between untrained and

trained young men, however, the untrained group showed significantly increased MDA and PC levels following an acute bout of exercise (GXT), which was not seen in the trained groups (resistance and endurance trained athletes). Furthermore, Zembron-Lancy et al. (2016), have shown that elderly inactive men had significant higher oxLDL and lower total plasma antioxidant status (TAS) compared to either the young inactive or elderly active group.

These results suggest that sedentary lifestyle is associated with enhanced vascular oxidative stress, which, in turn, propagates vascular dysfunction. Moreover, the alterations of inflammation and oxidative stress is more intense with aging and age-related diseases, such CVD.

Table 1: Acute Exercise Effects on Redox status

Exercise type	Study subjects	Training protocol	Findings	Reference
Acute Anaerobic exercise	Young males (n=16)	High intensity interval test on cycloergometer: 8 bouts of 1min at 100% of peak power Blood samples: pre, immediately post, 30min post exercise	↑TBARS 30min post exercise GSH, SOD not change ↓ CAT 30min post exercise ↓Lymphocyte proliferative	Gomes et al. 2016
Acute Aerobic exercise	Young males (n=30, age=21±2, 3 groups) WT=Well-trained group (n=10) MT=moderate trained group (n=10) UT=untrained group (n=10)	All groups performed an acute bout of aerobic exercise: 5min running with 50% VO2max & 30min running 70%Vo2max Blood samples: pre, immediately post, 10min post and 30min post exercise protocol.	↑GSH in MT compared with UT & WT groups ↓GSSG in MT compared with UT & WT groups ↑GSH/GSSG MT compared with UT & WT groups ↑Cortisol and CK → after exercise in all groups	Seifi-skishahr et al. 2016
Acute Aerobic exercise (test)	Healthy young males (3 groups): Competitive endurance athletes (ET) Resistanse trained athletes	Grated exercise test: Treadmill peak oxygen consumption test. Starting with 3% elevation for 3min and increasing 1.5% per min until exhaustion.	**Oxidative stress markers** **MDA and PC:** ↑ in UT group Not change in ET and RT groups	Park and Kwak, 2016

	(RT) Untrained individuals (UT)		**Antioxidant markers** **TAC:** ↓ in ET and RT groups ↓↓ in UT group	
<u>Acute</u> Aerobic exercise (swimming)	Male Wistar rats (6 groups):30 Control group (C): sedentary G3: below anaerobic threshold G4: below an. threshold. G5: an. threshold. G6: an. threshold. G8: above an. threshold.	1-h swimming carrying metal ring: 3% (G3), 4% (G4), 5% (G5), 6% (G6), 8% (G8) of their body weight	↑ lipid peroxidation (MDA) in trachea and lung in all exercise groups G3: ↑ MDA in rat trachea G4: ↑ MDA in rat trachea G5: ↑ MDA in rat trachea G6: ↑↑ MDA in rat trachea G8: ↑↑↑ MDA in rat trachea	Brito et al. 2015 (a)
<u>Acute</u> Aerobic exercise (swimming)	Male Wistar rats (6 groups):30 Control group (C): sedentary G3: below anaerobic	1-h swimming carrying metal ring: 3% (G3), 4% (G4), 5% (G5), 6% (G6), 8% (G8) of their body weight	↑ MDA in heart and aorta in all exercise groups G3: ↑ MDA in aorta & heart G4: ↑ MDA in aorta & heart	Brito et al. 2015 (b)

	threshold G4: below an. threshold. G5: an. threshold. G6: an. threshold. G8: above an. threshold.		G5: ↑ MDA in aorta & heart G6: ↑↑ MDA in aorta & ↑MDA in heart G8: ↑↑↑ MDA in aorta & heart	
<u>Acute</u> Anaerobic exercise	Healthy males (n=10)	CrossFit protocol: 5 pull-ups, 10 push-ups, 15 air-squats in 20min (as many rounds as possible) High intensity treadmill protocol: Running (90% HRmax) for 20min	immediately post, 1-h and 2-h post exercise Oxidative stress markers: ↑LOOH ↓PC Antioxidant capacity markers: ↑FRAP ↓TEAC	Kliszczewicz et al. 2015
<u>Acute</u> Resistance exercise	Chronic kidney patients (n=16)	Four Strength exercises in both lower limbs with ankle –cuffs and elastic bands (60% of 1-RM) 3 setsX10 rep, rest: 3min between each exercise and 1min between each set.	↓ SOD after acute exercise CAT, GPx, MDA and hs-CRP levels →not change	Esgalhado et al. 2015

Acute Resistance exercise	Males (n=16, age=25± 4, 2 groups) Untrained group (UT, n=8) Resistance trained group (RT, n=8)	Both groups performed one acute bout of a progressive RT protocol (leg extension) : 1x17 reps at 50% of 1RM, 1x14 reps at 60% of 1RM, 1x12 reps at 70% of 1RM, 2x5 reps at 80% of 1RM, 3x3 reps at 90% of 1RM, 5 min rest between each intensities, 90-120 sec. rest between sets. Blood collection: pre, immediately after each intensity, 30min post, 60min post, 24h post exercise bout	↑Blood lactate →parallel with the rise of ex. intensity in both groups. →post exerc. Return in baseline values ↑Protein Carbonyls (PC) during ex. bout and approached the baseline values in recovery period, in both groups Serum total glutathione (GSH) → no changes ↑SOD during ex. and 30min post ↑Lipid peroxidation (LHP) and approached the baseline values in recovery period, in both groups	Atabeck et al. 2015
Acute Aerobic exercise	Sedentary group (7 males & 8 females: age 65.8±3.3 y.) (score < 9 on the questionnaire of physical activity) corresponds to a sedentary life style. Active group (8 males & 10	Low intensity aerobic exercise: a) 5-10 min warm-up b)15-20 min aerobic exercises (walking, dancing, and aerobics) c)circuit muscular endurance exercise with elastic bands and free weights	**Rest:** 1) SOD: Higher levels for the active group compared with sedentary group. 2) α-Tocopherol: no differences between groups. 3) GR: no differences between groups. 4) MDA: no differences between groups. 5) GPX: no differences	Bouzid et al. 2014

	females: age 65.1±3.5 y.) (score 9-16 on the questionnaire of physical activity) corresponds to an active life style.	(knee flexion, arm raise, shoulder abduction, shoulder rotation, squatting, biceps curl etc.) rest 60-120 sec.	between groups. **20 min post exercise:** 1) SOD: Higher levels for the active group compared with sedentary group. 2) α-Tocopherol: no changes in sedentary group, ↑ in active group. 3) GR: no changes in both groups. 4) MDA: ↑ in both groups. 5) GPX: no changes in sedentary group, ↑ in active group.	
Acute Aerobic exercise	Women	A single bout of 30 min run, 70% VO2 max	↑ oxidative stress markers (Lipid hydroperoxides, protein carbonyls, GSH, GSSG, TNFa, interleukin 6)	Mckenzei MJ et al. 2014
Acute Aerobic exercise Anaerobic exercise	Trained men	A single bout of : a)60 min run, 70% HR reserve, b)5 X 60 sec. sprints, 100% max capacity, c) 10 X 15 sec. sprints, 200% max capacity d)No exercise rest	No effect on oxidative stress biomarkers (malondialdehyde, hydrogen peroxide, advance oxidation protein products), No effect on antioxidant status (trolox equivalent antioxidant capacity, superoxide dismutase, calatase, glutathione peroxidase)	Canale RE et al. 2014
Acute	Diabetes patients and	A single bout of a 3 hours walk, 30%	Oxidative stress remain constant in	Francescato, et

Aerobic exercise	healthy group	heart rate reserve	both groups ↑ anti-oxidant defense	al. 2014
<u>Acute</u> Aerobic and resistance exercise	Women (45-55y) Resistance group (RE): Followed 2 y resistance training program Aerobic group (AE): Followed 2 y aerobic training program Control group (C): sedentary women	Acute bout of exercise: RE: 10 rep. ~75-80% of 1RM X 10 stations AE: 50 min on cycle ergometer ~75-80% of HR C: No exercise Blood samples: pre, post, 1h post exercise	Rest: High levels SOD and CAT in RE and AE compared to C group. Post exercise: ↓ Antioxidant defense (↓ SOD and CAT in RE and AE) ↑ oxidative stress markers (↑ TBARS, protein carbonyl) 1h post exercise: ↓ Antioxidant defense (↓SOD and CAT in RE and AE) Oxidative stress: TBARS return at baseline levels, protein oxidation remains elevated	<u>A.M. Cardoso</u> et al. 2012
<u>Acute</u> Resistance exercise	Trained men	Acute bout of exercise: 7X4. 60-90% of 1RM	↑ urinary 8-OHdG excretion and plasma MDA levels	<u>Rahimi R</u>; 2011
<u>Acute</u> Resistance	Trained men	Acute bout of exercise:	↑ TBARS (42%), AOPP (28%), uric acid (27%) and GSH (14%), uric acid	<u>Deminice, R.</u>, et al. 2010

exercise		3X10 rep. ~75% of 1RM 90s rest between sets	(36%)	
<u>Acute</u> Resistance Exercise	Men	10 exercises X 9rep. ~75% of 1RM Blood samples: 30 min pre, immediately post exercise	↑ Lipid oxidation ↑ antioxidant concentrations	Ramel, et al. 2004
<u>Acute</u> Aerobic exercise	Sedentary group (4 males & 8 females) Active group (5 males & 8 females)	A single bout of 30 min run Sedentary: ~55% VO2max Active: ~70% VO2max	↑ oxidative stress (↓ lag time LDL oxidation) ↑ plasma MOP protein	Weitzstein et al. 1997

Table 2: Chronic Exercise Effects on Redox status

Exercise type	Study subjects	Training protocol	Findings	Reference
Chronic Resistance exercise (12 weeks)	Older adults (n=19, age≥60years, 2 groups) Control group(C, n=8) RT group (RT, n=11)	RT group performed: Supervised RT 3days/week 3 upper body exercises 4 lower body exercises 1set X 8-12 reps each exercise to volitional fatigue Muscle biopsies: pre, 48h post, after the last resistance exerc session at 3 & 12 weeks.	↑muscle strength Pyruvate oxidation, acid soluble metabolites and total fatty acid oxidation→ not change	Flack et al. 2016
Chronic Aerobic exercise (24 weeks)	Healthy older individuals (n=100, 2 groups) C= control group (n=50) EX= exercise group (n=50)	Moderate aerobic exercise: 45-60 min on treadmill, bicycle or Stair master, intensity 60-70% of HRmax, 3days/week.	Effects of exercise on Oxidative stress status: ↓MDA & 8-OHdG ↑TAC Inflammatory markers: ↓hs-CRP Significant correlation between oxidative stress markers and hs-CRP	Alghadir et al. 2016

Chronic Combine exercise training (16 weeks)	Healthy men (40-74 years, 2 groups): C= control group (n=26, no exercise, age: 52±9) Ex= exercise group (n=31, age: 58±10)	Ex group performed moderate combine exercise training: 3days/week, 60-75min/session consisted of: Aerobic ex: 25-30min/session (75% of HRR) Resistance ex:30-35 min/session (65-75% of 1 RM, 10-15 repsX3 sets, bench press, leg press, leg curl, leg extension, latissimus, abdominals, arm flexion) Stretching & cool down: 5-10min.	**Oxidative stress markers** ↓ **MDA** **Antioxidant markers** ↑ **TAC** **DNA damage in lymphocytes** ↓ DNA strand breaks ↓ oxidative DNA damage (FPG-sensitive sites) DNA repair capacity (8-oxoguanine DNA glycosylase) →not change	Soares et al. 2015
Chronic Aerobic exercise (6 weeks)	Male Wistar rats (4 groups): 28 C =Control group (n= 7) EX=Exercise group (n=7) D=Diabetes group(n= 7) EX+D=Exercise+Diabetes (n= 7)	Ex group and EX+D group: Free access to running wheel 24h/day for 6 weeks	↓MDA ↑ SOD , GPx, TAC	Naderi et al. 2015

Chronic Aerobic exercise (4 weeks)	Wistar rats (n=80, 8 groups) CS = control + sedentary, CE = control + exercise, CSQ = control + sedentary + quercetin, CEQ = control + exercise + quercetin, DS = diabetes + sedentary, DE = diabetes + exercise, DSQ = diabetes + sedentary + quercetin, DEQ = diabetes + exercise + quercetin.	CE, CEQ, DE & DEQ performed moderate chronic aerobic exercise (swimming) 1h/day, 5days/week.	After 4 weeks exercise intervention: ↓MDA & PC levels in aortic tissue in exercises group ↑SOD & CAT in aortic tissue in exercises groups ↓NOx levels in aortic tissue in exercises group ↓iNOx levels in aortic tissue in exercises group	Chis et al. 2015

Chronic Aerobic exercise (8 weeks, Swimming)	Rats (4 groups): 20 Healthy rats sedentary(H):5 Healthy + Exercise (H+Ex):5 High fat Diet sedentary (HFD):5 High fat Diet + EX (HFD+Ex):5	H+Ex and HFD+Ex group: 1-h Moderate intensity swimming for 8 weeks	H group: MDA in heart tissue →not change, LOX-1 protein → expressed in heart cells H+Ex group: MDA →not change, attenuated gene expression of LOX-1 receptor HFD group: ↑MDA, upregulated gene expression of LOX-1 receptor HFD+Ex group: ↓MDA, reduced gene expression of LOX-1 receptor	Riahi et al. 2015
Chronic Aerobic, resistance, flexibility training (12 months)	Healthy Male subjects (H) and with type 2 diabetes mellitus (3 groups): 30 Healthy group (H) Control group (CT2MD) Training group(ExT2MD)	ExT2MD group: moderate aerobic (cycling progressively increase 15min to 35min per session), resistance (major muscle groupsX3setsX12rep) and flexibility (Static stretching) training (total 140-270min/ week, gradually increased)	ExT2MD group: ↓oxPAPC compared with T2MD group, ↑oxPAPC compared with Healthy group T2MD group: ↑↑oxPAPC compared with Healthy group	Vinneti et al. 2015
Chronic Aerobic exercise	Male Wistar rats (4 groups): Sedentary Control (C, n=14) Exercise control (C-Ex, n=15)	Low intensity physical exercise training: Running duration 18min/day,	Lipid hydroperoxide: ↑in DM-C than C and DM-Ex Superoxide dismutase (SOD) and	Gimenes et al. 2015

(9 weeks)	Sedentary diabetes (DM-C n=25) Exercise diabetes (DM-Ex, n=25)	Speed 11m/min, 5days/week	Catalase ↓ in DM-C than C ↑ in DM-Ex than DM-C Glutathione peroxidase ↓ in DM-C than C and DM-Ex	
Chronic Aerobic exercise (10 days)	Sprague-Dawley rats (2 groups): Sedentary (SED) Endurance training group (Ex)	Exercise group: moderate intensity treadmill training Running duration 60/day Intensity 30m/min (70% max oxygen consumption)	24h after the final training Oxidative stress biomarkers: Lipid peroxidation 4-hydroxynonenal conjugated proteins (4-HNE) not differ between 2 groups Antioxidant capacity markers in ileum tissue: ↑ SOD2 ↑ CAT	Holland et al. 2015
Chronic Resistance exercise (12 weeks)	Male F344 rats (n=12, 2 groups) Sedentary/ control (C, n=6) Climbing exercise group (RT, n=6)	Progressive resistance exercise protocol: Climbing a ladder 135cm length (grid step 2.5cm, grade 60 degree) Weight load attached to their tails. 1st circle 50% of their body weight (Bw)	Aortic rings under 40X and 200X magnification: no significant difference between groups. In the aorta of rats: ↑ eNOS and AKT phosphorylation in RT group ↑ MnSOD and Redox factor-1 in RT	Li et al. 2015

		→2min rest 2nd circle 75% of their Bw → 2min rest 3rd circle 90% of their Bw → 2min rest 4th circle 100% of their Bw → 2min rest 5th circle 100% +30g of their Bw → 2min rest Training was stopped when rats refused to climb.	group ↓ FOXO1 phosphorylation in RT group	
Chronic Resistance exercise (4-16 weeks)	Wistar male rats (n=10, 3 groups) Sedentary –Control (C group) Exercise-1 (4weeks training, RT-1 group) Exercise-2 (16weeks training, RT-2 group)	Regular resistance exercise in a squat training device cylinder 4setsX12reps/day, 90min rest between each set, 5days/week	**Heart tissue:** ↑GPX only in Ex-2 group ↑MDA only in Ex-1 group SOD → no changes **Cell damage enzymes:** ↑LDH & CK → only in Ex-1 group	Ghiasi et al. 2015
Chronic	Sprague Dawley rats (n=60,	Exercise groups (Sh=ex, OVX+ex)	**Effects of exercise on:**	Tang et al.

Aerobic exercise (8 weeks)	4 groups) Sh=Sham sedentary group Sh+ex=sham with exercise OVX=ovariectomized sedentary group OVX+ex= ovariectomized with exercise group	performed aerobic exercise training: Running 15min/day for the 1st week and 60min/day at 18m/min for 7 weeks.	↑CSE expression in myocardium in OVX+ex group Anti-oxidative defense in myocardium: ↑TAC in OVX+ex group CAT & SOD →not change in OVX+ex group ↓CAT & SOD in sham+ex group Oxidative stress markers in myocardium: ↓MDA level in OVX+ex group	2016
Chronic Aerobic exercise (AE) Resistance exercise (RE)	Untrained men 3 groups: AE: n=10 RE: n=10 CT: n=10	AE: incremental running up to 80% of max HR RE: incremental RE beginning load 50% up to 80% of 1RM CT: Combination AE and RE every other	In all three training groups: ↑ SOD , erythrocyte GPx, TAC ↓ MDA No significant difference in the interaction of time and group	Azizbeigi, Kamal et al. 2014

Combined training (CT) (8 weeks)		day during the week	between variables of SOD and GPx enzymes and TAC of plasma and MDA.	
Chronic Aerobic exercise (12 weeks)	Rheumatoid arthritis patients	3 months, 3 sessions/week, 30-40 min/session, 70% VO2 max	No changes in markers of oxidative stress ↓ 3-Nitrotyrosine ↓disease activity	Wadley AJ et al. 2014
Chronic Aerobic exercise (16 weeks)	Obese & Type 2 Diabetes men	16 weeks, 3 sessions/week, 2 groups: a) low intensity (30-40% VO2max) b) moderate intensity (55-65% Vo2max)	No changes in body composition and aerobic fitness Improve oxidative stress markers especially when performed moderate intensity protocol.	Krause M, et al. 2014
Chronic Aerobic exercise	Postmenopausal women	Compared physical active with sedentary subjects, on oxidative stress markers.	↑ oxidative stress markers in sedentary versus active women	Bartfay W, Bartfay E, 2014
Chronic /Acute Aerobic exercise	Elderly men	Compared physical active with sedentary subjects, on oxidative stress markers, after an incremental exercise test	Low intensity aerobic exercise prevent the decline of antioxidants linked with aging	Bouzid MA, et al. 2013

Chronic Aerobic exercise (16 weeks)	Women	16 weeks, 5days/week, 30 min/session, 80-85% HRmax	No changes: Body weight & BMI, ↑ aerobic fitness ↓systemic oxidative stress only in women with the highest quartile of plasma F2-isoprostanes at baseline (≥57pg/mL)	Arikawa et al. 2013
Chronic Combined aerobic and resistance exercise (6 weeks)	Women with metabolic syndrome	6 weeks, 3 sessions/week, 60-min/session aerobic and strength exercises	↓ indicators of oxidative stress, arterial pressure levels, pulse pressure and the Augmentation Index ↑ aerobic fitness	Silva MA et al. 2013
Chronic Aerobic exercise (12 weeks)	Spontaneously hypertensive rats	12 weeks, 5days/week, 60 min/session, 55-65% max running speed	↓ oxidative stress ↑ NO bioavailability ↓ blood pressure Improve mechanical and functional alterations of the coronary and small mesenteric arteries	Roque R et al. 2013

Chronic Resistance exercise (6 weeks)	Healthy young individuals (n=32, 2 groups): African Americans (AA, n=14) Caucasian (Cau, n=18)	Moderate RT: 3 sessions/week, 60min/session 2-way body part split: legs, back and biceps on one day; chest, shoulder and triceps on a separate day.	↑ Strength in both groups ↓ blood pressure in Cau blood pressure in AA→ not change ↓ MMP-9 in AA MMP-9 in Cau→ not change ↓ 8-isoprostane (8-IsoP) in AA IL-10, TNF-a, sVCAM-1, MMP-2→ not change in either group	Cook et al. 2013
Chronic Aerobic exercise (8 weeks)	Adult rats	8 weeks, 5 days/week, 60 min/session, 60% max running speed	↑ running distance ↑antioxidant defense system ↑superoxide dismutase (SOD)	Coelho CW et al. 2013
Chronic Resistance exercise (6 weeks)	Young men	6 weeks, 3 days/week 2 groups: Hypertrophy-intensity group (3X12 rep. ~70% of 1RM) strength-intensity group (six exercises	In both groups: ↓MDA ↑GSH	Cakir-Atabek H et al. 2010

		of 3 setsX6 rep. ~85% of 1RM)		
Chronic Resistance exercise (RE) (8 weeks)	Men	Progressive resistance-training 8 RE on nonconsecutive days for 8 weeks at 50% of 1RM and reached 80% 1RM by Week 8	↑ SOD ↓ MDA No significant differences in erythrocyte GPx, TAC levels	Azizbeigi K et al. 2013
Chronic Resistance exercise (RE) (8 weeks)	Men	moderate (MR) and high resistance (HR) training	↑ SOD activity in MR (p = 0.026) and HR (p = 0.044) groups. ↑ GPX activity in HR (p = 0.012) and MR (p = 0.037) ↓ MDA in MR (p = 0.013) and HR (p = 0.023) no significant difference in IL-6, TNF-α and CK occurred between groups.	Azizbeigi K et al. 2015
Chronic Resistance	Rats 4groups: a) resistance training b) resistance	6 weeks, 3 days/week Rise onto their hind limbs while wearing lead-weighted vests 30 times	Alcohol treatment in the sedentary animals: ↑cardiac malondialdehyde, lipid peroxidation, ↓index of myocardial	Chicco AJ, et al. 2006

exercise (6 weeks)	training + alcohol treatment (35% of kilocalorie intake) for 6 weeks c) sedentary d) sedentary + alcohol treatment	per training session	antioxidant potential compared with all other groups.	
Chronic Resistance exercise (24 weeks)	Untrained healthy individuals (n=49, age=60-72, 4 groups) Control normal weight group (no exercise, Cn) Control obese group (no exercise, Co) Exercise normal weight group (RTN group) Exercise obese group (RTO group)	RTN & RTO group performed moderate RT program: One set of 13 exerc. X8-13reps (50-80% of 1RM) 3days/week	↑muscle strength, VO2max in RTN & RTO group Total cholesterol and HDL-C: no significant differences ↓Lipid hydroperoxides and TBARS→ lower in RTN & RTO group compared with Cn & Co Homocysteine in plasma → lower values in RTN & RTO group compared with Cn & Co	Vincent HK et al. 2006
Chronic Resistance exercise (12 weeks)	elderly men	12 weeks, 3 sessions/week, 3 sets X 10 repetitions each of leg press and leg extension (50-80% 1RM)	↑ muscle antioxidant capacity (82,5% catalase activity, 75% CuZnSOD activity)	Parise et al. 2005

Chronic Resistance exercise (14 weeks)	elderly men and women	14 weeks whole body regular resistance exercise	↓ 8-OHdG No changes: Protein content for CuZnSOD, MnSOD, and catalase, and enzyme activities for citrate synthase, mitochondrial ETC complex I+III, and complex II+III	Parise G et al. 2005
Chronic Aerobic exercise (9 weeks)	Male wistar rats	9 weeks, 5 sessions/week, 60min/session for 6weeks and 90min/session for 3w	No changes: TBARS, reactive carbonyl derivatives content, ↓ 8-OHdG ↑ DT-diaphoase and proteasome complex	Radak et al. 1998

III. METHODOLOGY

3.1. Participants

Sixty malepatients (n=60) with coronary artery disease, volunteered to participate in this study. All participants had previously experienced a myocardial infraction or had undergone coronary artery bypass grafting or percutaneous transluminal coronary angioplasty.
Initially, a thorough history and physical examination as well as both resting and exercise standard echocardiography and ECG were obtained in all study subjects before entering the study.

The presence of angina or other significant symptoms (e.g. unusual shortness of breath, light headedness or dizziness), the presence of pathologic ECG-changes at rest or during exercise stress test, as well as technical limitations such as poor echocardiographic image quality, uncontrolled congestive heart failure, uncontrolled diabetes mellitus, unstable dysrhythmia and uncontrolled systemic hypertension were considered to be exclusion criteria. Furthermore, patients with arthritis or other myoskeletal and inflammatory diseases as well as patients under anti-inflammatory drugs or using tobacco products were also excluded.

All subjectsare consideredas low-risk patients according to the following criteria of the American Association of Cardiovascular and Pulmonary Rehabilitation: 1) absence of angina or other significant symptoms (e.g., unusual shortness of breath, light-headedness, or dizziness heart rate and systolic blood pressure with increasing workloads and recovery) 2) absence of arrhythmias 3) absence of signs or symptoms of ischemia or congestive heart failure 4) absence of clinical depression 5) functional capacity ≥7 metabolic equivalents (METs) 6) uncomplicated myocardial infraction or revascularization procedure and 7) presence of normal hemodynamics during exercise testing and recovery (i.e., appropriate increases and decreases in heart rate and systolic blood pressure with increasing workloads and recovery), blood pressure <160/90 mm Hg with or without medication, 8) ejection fraction > 50% at rest 9) medically stable (The ESC Textbook of Preventive Cardiology, Stephan Gielen et al. 2016).

All subjects were informed about the nature of the study, the associated risks and benefits and they signed a consent form. Procedures were approved by the Cyprus National Bioethics Committee and were completed in accordance with the declaration of Helsinki.

3.2. Testing procedures

Anthropometric measurements, systolic and diastolic blood pressure, blood analyses, flexibility, isometric peak torqueand cardiovascular stress testing were performed at baseline, after 4, 8, 9, 10 and 11.

3.2.1. Anthropometric measurements

3.2.1.1. Body mass &Height

Body mass (Kg), height (cm), were measured using a scale (Beam Balance 710, Seca, United Kingdom) and a stadiometer (Seca model). Body mass was measured to the nearest 0.5 kg with subjects wearing their underclothes and being barefooted. Standing height was measured to the nearest 0.5 cm. Body mass index (BMI) was calculated as the weight (kg) over the height squared (m^2). Percent body fat was calculated from 7 skinfold measures (average of 2 measurements of each site) using a Harpenden caliper.

3.2.1.2. Waist & Hip circumferences

Waist and hip circumferences were measured according to the World Health Organisation's data gathering protocol (WHO, 2012). The waist circumference was assessed at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest, using a stretch-resistant tape that provides a constant 100 g tension. Hip circumference was measured around the widest portion of the buttocks, with the tape parallel to the floor.

3.2.1.3. Systolic and diastolic Blood pressure

Systolic and diastolic blood pressure was measured according to a standardized procedure with the participant in the supine position using a calibrated, manual sphygmomanometer and stethoscope after 5 minutes rest, using the first and fifth Korotkoff sounds, according to American Heart Associationstandards.

3.2.2. Blood analyses

Blood samples were obtained under the same conditions, after anovernight fast (between 08:00 – 09:00 h). Blood samples were drawn from an antecubital arm vein using a 20-gauge disposable needle equipped with a Vacutainer tube holder (Becton Dickinson, Franklin Lakes, NJ,USA) with the subject in a seated position. Samples (8 mL) were collected into a Vacutainer tube. Blood was allowed to clot for 30 min at room temperature and subsequently centrifuged at 2000 *g, 4 ^{o}C* for 15min for clear separation of serum. The serum

layer was removed and the resulting serum was placed into separate microcentrifuge Eppendorf™ tubes in multiple aliquots and frozen at – 80 $^{o}C$for later analyses.
Both plasma and the red blood cell lysate were used to determine total antioxidant capacity (TAC), thiobarbituric acid reactive substances (TBARS), catalase (CAT), reduced glutathione (GSH), oxidized glutathione (GSSG) and protein carbonyls (PC).

3.2.3. Flexibility of the lower back and hamstring muscles

The flexibility of the lower back and hamstring muscles, was assessed by a sit-and-reach test. Subjects sat on the floor with their hips, back and occipital region of the head touching a wall, and their legs held straight at 90° in front of the upper body. The zero point of the device was set in this position. Subjects then slowly bent forward and as far as possible while pushing the device with both hands. Once the farthest distance was reached, participants held the position for 2 seconds. Measurements were performed two times, and the maximum value was used in final analyses.

3.2.4. Isometric muscle testing

Maximal isometric peak torque of knee extensors (IPTE)of the right leg,at 60° of knee joint flexion(where 0° corresponded to full knee extension) was measured on a computer-controlled isokinetic dynamometer (Cybex Norm Lumex, Ronkonkoma, NY, USA). Before the assessment of isometric peak torque, volunteers warmed up for 8 minutes on a cycle ergometer (Excite, Technogym, Italy), followed by 3 minutes of stretching exercises. All subjects were familiarized with the isokinetic dynamometer and the testing procedures by performing four consecutive submaximal (<50% max) isometric warm-up repetitions. Three maximal trials(3-second duration) separated by a 60-second rest interval between attempts were then performed, with the maximal peak force (Nm) recorded.Visual feedback and verbal encouragement were given during the trials.

3.2.5. Cardiovascular stress testing

VO_{2max} was used as a measure of cardiorespiratory fitness. VO_2 max was performed according to the Bruce protocol(Bruce RA andHornsten, 1969), using a graded multistage treadmill.Respiratory gases were collected and measured using Ultima™ CardiO2 gas exchange analysis system (St. Paul, Minnesota, USA). The incremental treadmill test to exhaustion and the accompanying gas collection procedures have been previously described in detail (Hall-López JA et al. 2015).Briefly, each subject started walking at 2,7 km/hr and at a

gradient of 10%. Each ensuing work level lasted three minutes, during which the grade was increased 2%.Speed and gradient were then incrementally increased every stage with the intent of reaching the subject's maximal exercise capacity within 6 to 12 min.At three minute intervals, the incline of the treadmill was increased by 2%, and the speed was increasedby approximately ~1.5km/hr.

Twelve lead electrocardiogram (ECG), heart rate and blood pressure were obtained during each stage of the test and for at least 5 minutes after exercise.Patients were encouraged to exercise to the maximum of their physical capacity unless chest pain, significant ST segment depression, arrhythmia, or non-cardiac symptoms led to premature termination of their exercise.The stress test was terminated when subjects indicated fatigue or if the ECG indicated an abnormal rhythm or ischemia.

VO2max was determined when three of the following four criteria were met: (i) volitional fatigue, (ii) a < 2 mL.kg-1.min-1 increase in VO2 with an increase in work rate, (iii) a respiratory exchange ratio ≥1.10, and (iv) the patient achieved at least 85% of the theoretical maximum HR (220 - age). Gas analyzer was calibrated immediately before each subject's test. Peak oxygen consumption (VO2) was determined as the highest 20-s average value of VO2 observed over the last 60 s of exercise.

3.2.6. Study Protocol

After the pre-training testing procedures, subjects were randomly assigned to a control group (C), an aerobic training group (AT), a resistance training group (RT), or a combined training group (CT). Each of the three training groups (AT, RT, and CT) followed a supervised training program three days per weekon non-consecutive days, for eight months.

3.2.6.1. Experimental Groups

i) **Control group** (C, n = 15):

Patients in this group did not undergo any formalized physical training. They completed all testing procedures that the training groups performed at baseline, after 4, 8, 9, 10 and 11 months as briefly described before, while maintaining their current activity levels.

ii) **Aerobic training group** (AT, n = 15):

Participants in the AT group performed four intervals of 10 min on a treadmill or a cycle ergometer (Excite, Technogym, Italy) at 60–75% HRmax, interspersed by 6 min recovery periods, 3 days a weekon non-consecutive days, for 8 months.Treadmill and cycle ergometer speed were adjusted on an individual

basis to ensure patients exercised at their prescribed exercise intensity based on each patient's target heart rate, obtained from each subject's maximal oxygen uptake (VO2max) test as described in detail before, at baseline and four months. Before each training session, volunteers warmed up for 5 minutes on a cycle or on a treadmill ergometer, followed by 3 minutes of stretching exercises, and each training session was followed by 5 min cool-down.

iii) **Resistance training group** (RT, n = 11):

The RT group performed upper and lower body resistance exercises using 8 circuit weight training machines (Table I). RT protocol consisted of 50-60 min of circuit weight training per day, 3 days a weekon non-consecutive days, for 8 months.

This training was circularly performed in 8 exercise stations and included 1 set with 12-15 repetitions at 60% of 1-RM in each station. Each exercise station (set) and circuit was separated by 60-90 sand 5 min rest respectively.Specifically, participants performed 12-15 repetitions in each station, rested for 60 to 90 seconds and then moved to the next machine until they complete one circuit, followed by 5 min rest. In each exercise session were completed two circuits.

Table 3. Circuit Weight Stations

Arms and upper torso
Chest press
Shoulder press
Pulley row
Core muscles
Total abdominal
Rotary torso
Legs
Leg press
Leg extension
Leg curl

Before each training session, volunteers warmed up for 5 minutes on a cycle or on a treadmill ergometer (Excite, Technogym, Italy), followed by 3 minutes of stretching exercises, and each training session was followed by 5 min cool-down.

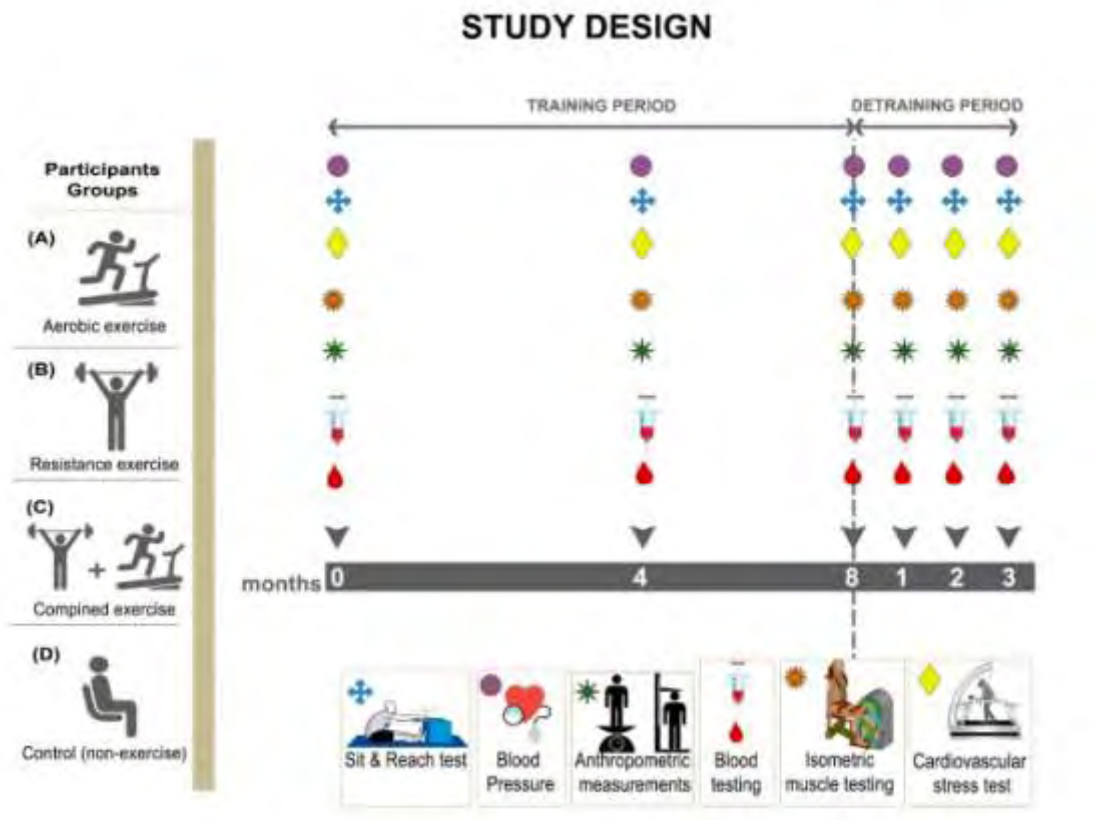
One-repetition maximal strength was measured on the 8 circuit weight training machines at baseline and four months, to adjust the training intensity. Strength was recorded as the maximal number of pounds lifted in one full range of motion.

iv) **Combine training group** (CT, n = 15): The CT group performed

Participants in the CT group performed both the aerobic and the resistance exercise programs on the same day, during the same session, and exercised approximately 50-60 min/per day, 3 days a weekon non-consecutive days, for 8 months.

In each combine exercise session were completed twoaerobic intervals of 10 min on a treadmill or a cycle ergometer and one weight trainingcircuit, utilizing the same intensities and recovery periods used by the AT and RT groups. All sessions included a 5 min warm-up, 3 min stretch exercises, and a 5 min cool-down.

Figure 2. Study Design



3.3. Complications

Of the 60 participants that volunteered to participate in this study, only 56 completed the study and were included in the statistical analysis.In the aerobic exercise group, one patient did not perform more than 10% of the exercise sessions and was excluded from the statistical analysis. In the resistance exercise group, three patients were unable to complete

the 8 months training sessions and follow-up testing procedures, because one of them had muscle injury and two of them for personal reasons. These four patients are not included in the subsequent statistical analysis or reported values.

No sustained arrhythmias or other cardiovascular complications were observed in any of the patients during exercise.

IV. RESULTS

4.1. Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics 8 (IBM Corporation). After testing whether data were normally distributed (Shapiro–Wilk test), an analysis of variance (ANOVA) with repeated measures for time (pre-training, 4 month training, 8 month training, 1 month detraining, 2 month detraining and 3 month detraining) and group (aerobic, resistance, combine and control) was performed. In the case of non-homogeneity of variances revealed by the Mauchly's sphericity test ($p<0.05$), the Greenhouse–Geisser correction was used to assess significant main effects. Where significant main effects were observed, Bonferroni's post hoc correction ($p<0.05$) was used to aid interpretation of these interactions.

4.2. *Subjects characteristics*

There were no differences between the four groups of participants in relation to the baseline characteristics (table 4a, b, c). After training, statistically significant differences were found, in relation to body mass, body fat, waist and hip circumferences and blood pressure, which were changed during training and detraining period.

4.2.1. Body mass

After 4 months of training, body mass significantly decreased ($P<0.001$) for all exercise groups(aerobic, resistance and combined) and remained decreased ($P<0.001$) until the end of the 3rd month of the detraining period (table 4a).

4.2.2. Body fat

After 4 months of training, body mass significantly decreased ($P<0.001$) for all exercise groupsand remained decreased ($P<0.001$) until the end of the 1st month of the detraining period (table 4a).

4.2.3. Waist and hip circumferences

After 4 months of training, waist circumferences significantly decreased (P<0.05) for the control, aerobic and combined exercise groups, but not for the resistance exercise group. Waist circumferences subsequently increased for these groups and after 8 months theywere restored to the baseline values. However, there were no differences between the four groups of participants in relation to the waist to hip ratio, durining the training and the detraininh period. (table 4b).

4.2.4. Systolic and diastolic Blood pressure

After 4 months of exercise training, systolic blood pressure (SBP) significantly decreased for the aerobic exercise group (P<0.05) and for the combined exercise group (P<0.05) and remained decreased (P<0.05) until the end of the 3rd month of the detraining period. In the resistance exercise training group, SBP significantly decreased (P<0.05) after 8 months of exercise training, however at the end of the 1st detraining period itwas restored to the baseline values. Diastolic blood pressure (DBP) significantly decreased (P<0.05) after 4 months only in aerobic exercise training group and it remained decreased until the end of the 3rd month of the detraining period (table 4c).

4.3. Physical Fitness

4.3.1. Flexibility of the lower back and hamstring muscles

After 4 and 8 months of exercise training, flexibility significantly increased (P<0.05) in the aerobic and combined exercise training groups. After training cessation, the flexibility scoredropped near the pre exercise levels for the aerobic exercise group, remained high for the combined exercise group (p<0.05) and significantly decreased (p<0.05) for the resistance exercise group, until the end of the second month of the detraining period (table 5).

4.3.2. VO2max

After 4 and 8 months of exercise training, VO2max significantly increased (P<0.05) in the aerobic exercise training group andremained high at the end of the 1st detraining period, but it was not statistically significant. However, at the end of the 2nd month of the detraining period, VO2max for the aerobic exercise group significantly increased (P<0.05), whereas at the end of the 3rd detraining period it was restored near the pre exercise levels. VO2max significantly increased (P<0.05) after 8 months of resistance exercise training and it remained increased (P<0.05), until the end of the 3rd month of the detraining period. There were no improvements in VO2maxfor the combined exercise training group(table 6).

4.3.3. Isometric Peak Torque

After 4th months of exercise training, isometric peak torque significantly increased for the aerobic exercise group ($P<0.05$), the resistance exercise group ($P<0.001$) and for the combined exercise group ($P<0.001$). These alterations remained high for all exercise groups until the end of the third detraining period. Isometric peak torque significantly decreased for the control group ($P<0.05$) at the end of the 1st detraining period (table 7).

Table 4a. Physical characteristics (Body mass & Body fat)

	Training				Detraining		Main effects and interactions		
	Baseline	Month 4	Month 8	Month 1	Month 2	Month 3	G	T	G × T
Body mass (Kg)									
Aerobic	87.5 ± 2.9	85.8 ± 2.1*	84.8 ± 2.2*	85.2 ± 2.2*	85.5 ± 2.2*	85.8 ± 2.2*	NS	P<0.001	P<0.001
Resistance	88.7 ± 3.6	87.1 ± 3.8	86.5 ± 3.9*	87.1 ± 3.5	87.6 ± 3.9	87.6 ± 3.9			
Combined	85.2 ± 2.1	82.4 ± 2*	81.5 ± 2.1*	82.1 ± 2*	82.5 ± 2*	82.63 ± 2.03*			
Control	86 ± 3.6	86.2 ± 3.5	86.1 ± 3.7	85.6 ± 3.6	85.8 ± 3.7	86.07 ± 3.71			
Body fat (%)									
Aerobic	33.6 ± 0.7	32.7 ± 0.7*	32.2 ± 0.7*	32.9 ± 0.7*	33.1 ± 0.7	33.2 ± 0.8	NS	P<0.05	NS
Resistance	33.5 ± 0.5	32.8 ± 0.5*	32.4 ± 0.2*	32.7 ± 0.6*	33.1 ± 0.6	33.2 ± 0.5			
Combined	32.9 ± 0.6	32.4 ± 0.5*	31.9 ± 0.5*	32.1 ± 0.5*	32.4 ± 0.5	32.5 ± 0.5			
Control	31.6 ± 1.2	31.4 ± 1.1	31.4 ± 1.2	31.3 ± 1.1	31.6 ± 4.3	31.3 ± 1.2			

G×B: 2-way interaction for group and bout; G×T: 2-way interaction for group and time; G: Main effect of training group; T: Main effect of time.

*Significantly different from the baseline value in the same group ($P < 0.05$).

Table 4b. Physical characteristics (Waist & Hip circumferences)

	Training			Detraining		
	Pre	Month 4	Month 8	Month 1	Month 2	Month 3
HIP(cm)						
Aerobic	100,1 ± 2,39	99,0 ± 2,63	100,1 ± 2,48	99,5 ± 2,75	98,2* ± 2,82	97,8* ± 2,69
Resistance	100,7 ± 2,46	98,5* ± 2,60	99,6 ± 2,95	100,0 ± 2,63	98,9 ± 2,69	98,6* ± 2,79
Combined	95,7 ± 1,91	93,7* ± 2,22	95,3 ± 2,30	95,3 ± 2,25	94,1 ± 2,07	93,6* ± 2,10
Control	95,4 ± 3,16	94,4 ± 3,25	95,6 ± 3,74	94,2 ± 3,50	93,4* ± 3,02	92,7* ± 3,57
WAIST (cm)						
Aerobic	104,2 ± 2,36	102,8* ± 2,35	103,4 ± 2,48	103,2 ± 2,76	102,1* ± 2,39	102,2* ± 2,06
Resistance	103,4 ± 3,26	102,3 ± 3,38	102,4 ± 3,37	102,2 ± 3,46	102,1 ± 3,40	101,4 ± 3,41
Combined	98,8 ± 1,90	97,0* ± 2,14	97,8 ± 2,12	97,1 ± 2,09	96,7* ± 1,96	96,1* ± 1,91
Control	98,9 ± 4,57	96,9* ± 4,35	98,3 ± 5,14	97,0* ± 4,74	95,9* ± 5,14	95,9* ± 5,04
WAIST/HIP						
Aerobic	1,04 ± 2,4	1,04 ± 2,5	1,03 ± 2,5	1,04 ± 2,8	1,04 ± 2,6	1,04 ± 2,4
Resistance	1,03 ± 2,9	1,04 ± 3,0	1,03 ± 3,2	1,02 ± 3,0	1,03 ± 3,0	1,03 ± 3,1
Combined	1,03 ± 1,9	1,04 ± 2,2	1,03 ± 2,2	1,02 ± 2,2	1,03 ± 2,0	1,03 ± 2,0
Control	1,04 ± 3,9	1,03 ± 3,8	1,03 ± 4,4	1,03 ± 4,1	1,03 ± 4,1	1,03 ± 4,3

* Sig vs. pre in the same group ($p<0.05$)

Table 4c. Physical characteristics (Systolic & Diastolic Blood Pressure)

	Training			Detraining		
	Baseline	Month 4	Month 8	Month 1	Month 2	Month 3
Systolic blood pressure (mmHg)						
Aerobic	140,28 ± 5.07	127,22* ± 3.92	128,33* ± 4.13	127,22* ± 5.12	129,17* ± 5.40	130,83* ± 4.07
Resistance	138,64 ± 7.21	130,91 ± 4.11	122,73* ± 3.42	126,82 ± 3.48	130,91 ± 4.05	134,55 ± 5.02
Combined	151,56 ± 7.64	128,75* ± 4.65	123,44* ± 3.20	129,06* ± 3.12	128,44* ± 3.32	129,06* ± 3,91
Control	136,67 ± 4.21	135,33 ± 3.89	137,33 ± 4.39	136,33 ± 4.72	133,67 ± 5.09	132,33 ± 2.86
Diastolic blood pressure (mmHg)						
Aerobic	83,33 ± 2,36	78,89* ± 2,14	78,72* ± 1,63	79,44* ± 2,29	79,17* 1,36	80,00* ± 0,54
Resistance	81,36 ± 2,25	81,82 ± 1,46	78,18 ± 2,58	78,64 ± 1,02	78,64 ± 1,24	79,55 ± 1,49
Combined	82,81 ± 2,79	80,63 ± 1,71	79,69 ± 2,06	80,94 ± 1,52	81,25 ± 0,75	81,25 ± 0,96
Control	81,67 ± 2,33	82,33 ± 1,65	83,33 ± 1,74	81,67 ± 1,85	81,33 ± 1,72	81,67 ± 1,96

* Sig vs. pre in the same group ($p<0.05$)

	Training			Detraining		
	Pre	Month 4	Month 8	Month 1	Month 2	Month 3
Aerobic	23,25 ± 1,80	25,33* ± 2,04	27,39* ± 2,05	24,56 ± 2,11	24,00 ± 1,81	23,72 ± 1,78
Resistance	27,27 ± 1,97	25,64 ± 1,88	26,14 ± 1,87	24,86* ± 1,69	24,82* ± 1,65	26,45 ± 1,60
Combined	24,75 ± 2,72	27,13* ± 2,62	28,28* ± 2,75	26,63* ± 2,79	25,81 ± 2,96	25,94 ± 2,85
Control	23,67 ± 1,73	22,27 ± 1,70	23,67 ± 1,65	22,70 ± 1,10	23,40 ± 1,03	23,27 ± 1,26

Table 5. Flexibility of lower back muscles and hamstrings (cm)

* Sig vs. pre in the same group ($p<0.05$)

Table 6. VO2max *(ml/Kg/min)*

	Training			Detraining	
	Pre	Month 4	Month 8	Month 1	Month 2	Month 3
Aerobic	25.15 ± 0.99	26.75* ± 1.13	27.35* ± 1.09	26.79 ± 1.19	28.33* ± 1.16	26.52 ± 1.17
Resistance	22.38 ± 1.44	24.66 ± 1.66	25.63* ± 1.59	25.86* ± 1.73	27.11* ± 1.69	25.31* ± 1.71
Combined	25.44 ± 1.23	26.55 ± 1.41	27.11 ± 1.36	26.64 ± 1.48	27.49 ± 1.45	26.05 ± 1.46
Control	27.3 ± 1.13	26.35 ± 1.30	27.01 ± 1.25	27.92 ± 1.36	27.77 ± 1.33	27.12 ± 1.34

* Sig vs. pre in the same group ($p<0.05$)

Table 7: Isometric Peak Torque (Nm)

	Training			Detraining		
	Pre	Month 4	Month 8	Month 1	Month 2	Month 3
Aerobic	172.3 ± 10.1	184.1* ± 9.5	189.6* ± 9.3	183.0* ± 9.2	180.1* ± 9.1	179.0* ± 9.4
Resistance	176.2 ± 12.9	211.0# ± 12.2	230.2# ± 11.9	231.1# ± 11.8	216.0# ± 11.6	208.4# ± 12.0
Combined	182.9 ± 10.8	212.0# ± 10.1	219.5# ± 9.9	209.8# ± 9.8	201.8* ± 9.6	199.9* ± 10.0
Control	168.7 ± 11.1	170.5 ± 10.4	166.8 ± 10.2	160.5* ± 10.1	165.7 ± 9.9	169.7 ± 10.3

Sig vs. pre in the same group ($p<0.001$)

* Sig vs. pre in the same group ($p<0.05$)

4.4. Redox status

The results forbiomarkers of oxidative stress in red blood cell lysate, plasma and serum are presented in tables 8 and 9. Changes to redox status are reported as percentages in annex tables (p. 104-106).

Biomarkers of oxidative stress in Plasma and Serum

There were no significant differences between groups at pre exerciselevelsas far as biomarkers of oxidative stress in plasma and serum are concerned.

TBARS levelssignificantly decreased (P<0.05) from pre exercise levels to after 4 monthsof exercise training for the aerobic and combined exercise groups, but not for the other two groups (resistance and control).The TBARS activity subsequently increased for both groups (aerobic and combined) and after 8 months it was restored to the pre exercise levels.

After 4 and 8 months of training, TAC levels were significantly increased (P<0.001) compared to the pre exercise levelsfor all exercise groups (aerobic, resistance and combined).During the 1st month of detraining, TAC levelsdropped near the pre exercise values for all groups.However, at the 2nd month of the detraining period, TAC values significantly increased (P<0.05) and remained increased (P<0.05) until the end of the 3rd month of the detraining period for the aerobic exercise group.

Biomarkers of oxidative stress in Red Blood Cell Lysate

There were no significant differences between groups regarding pre values for biomarkers of oxidative stress in red blood cell lysate.In the aerobic exercise group GSH has shown significant increase, whereas the GSSG has decreased. As a result of the aerobic exercise, glutathione-glutathione disulfide ratio (GSH/GSSG) has significantly increased. More specifically, after 4 and 8 months of aerobic exercise training, GSH levels tended to increase compared to pre exercise levels (p = 0.08).After training cessation, GSH levels dropped near the pre exercise levels. GSSG levels significantly increased (P<0.05) at 4 and 8 months of aerobic exercise training. After 8 months, GSSG levels subsequently increased, and they were restored to the pre exercise levels at the end of the 1st detraining period. The ratio of GSH/GSSG significantly increased after 4 (P<0.001) and 8 months (P<0.05), only for the aerobic exercise group. However, in the combined exercise group, the ratio of GSH/GSSG was significantly decreased (P<0.05) at the end of the 3rd detraining period.

Table 8. Biomarkers of oxidative stress in Plasma and Serum (TBARS & TAC)

	Training			Detraining	
	Pre	Month 4	Month 8	Month 1	Month 2	Month 3
TBARS						
Aerobic	5,565 ± 0,529	3,378* ± 0,558	5,554 ± 0,593	6,274 ± 0,534	5,97 ± 0,448	5,908 ± 0,716
Resistance	6,164 ± 0,794	4,415 ± 0,837	5,986 ± 0,89	7,481 ± 0,801	6,784 ± 0,672	6,708 ± 1,075
Combined	6,474 ± 0,58	4,776* ± 0,612	6,273 ± 0,65	7,357 ± 0,585	6,079 ± 0,491	7,473 ± 0,785
Control	5,636 ± 0,561	5,373 ± 0,592	5,782 ± 0,629	6,791 ± 0,566	6,784 ± 0,475	6,386 ± 0,76
TAC						
Aerobic	0,965 ± 0,029	1,129# ± 0,025	1,194# ± 0,021	0,96 ± 0,029	1,042* ± 0,025	1,056* ± 0,024
Resistance	0,929 ± 0,037	1,145# ± 0,032	1,115# ± 0,027	0,938 ± 0,037	1,012 ± 0,032	1,016 ± 0,03
Combined	0,997 ± 0,032	1,171# ± 0,027	1,161# ± 0,023	1,025 ± 0,032	1,04 ± 0,028	1,046 ± 0,026
Control	1,101 ± 0,031	1,132 ± 0,027	1,135 ± 0,022	1,076 ± 0,031	1,058 ± 0,027	1,014 ± 0,025

* Sig vs. pre in the same group ($p<0.05$)

Sig vs. pre in the same group ($p<0.001$)

Table 9a. Biomarkers of oxidative stress in Red Blood Cell Lysate (GSH, GSSG, GSH/GSSG)

	Training				Detraining		**Main effects and interactions**
	Pre	Month 4	Month 8	Month 1	Month 2	Month 3	
GSH							
Aerobic	3,839 ± 0,549	5,157* ± 0,456	5,161* ± 0,57	3,819 ± 0,366	3,346 ± 0,325	3,622 ± 0,539	
Resistance	3,961 ± 0,702	4,975 ± 0,583	4,059 ± 0,729	2,957 ± 0,468	2,83 ± 0,416	3,425 ± 0,69	* Approached Sig vs. pre p=0.08
Combined	4,21 ± 0,601	4,621 ± 0,499	4,181 ± 0,624	3,559 ± 0,401	3,96 ± 0,356	3,204 ± 0,591	
Control	4,249 ± 0,582	4,36 ± 0,483	3,454 ± 0,604	3,583 ± 0,388	3,659 ± 0,345	3,466 ± 0,572	
GSSG							
Aerobic	1,277 ± 0,078	1,022* ± 0,107	1,065* ± 0,116	1,036* ± 0,103	1,214 ± 0,077	1,393 ± 0,083	* Sig vs. pre p<0.05;
Resistance	1,104 ± 0,099	1,138 ± 0,137	1,079 ± 0,149	1,014 ± 0,132	1,179 ± 0,098	1,31 ± 0,106	
Combined	1,177 ± 0,085	1,047 ± 0,117	1,062 ± 0,128	1 ± 0,113	1,264 ± 0,084	1,316 ± 0,09	
Control	1,247 ± 0,085	1,198 ± 0,117	1,189 ± 0,128	1,206 ± 0,113	1,246 ± 0,084	1,258 ± 0,09	
GSH/GSSG							
Aerobic	3,092 ± 0,432	6,033# ± 0,851	4,827* ± 0,575	3,379 ± 0,406	2,844 ± 0,377	2,718 ± 0,398	* Sig vs. pre p<0.05;
Resistance	3,826 ± 0,552	4,747 ± 1,088	3,492 ± 0,736	2,464 ± 0,519	2,305 ± 0,482	2,593 ± 0,509	# Sig vs. pre p<0.001
Combined	3,999 ± 0,473	5,039 ± 0,932	4,485 ± 0,63	3,701 ± 0,444	3,313 ± 0,413	2,524* ± 0,436	
Control	3,407 ± 0,473	3,563 ± 0,932	3,307 ± 0,63	3,619 ± 0,444	3,387 ± 0,413	2,531 ± 0,436	

Protein Carbonyls (PC), significantly decreased for the aerobic exercise group ($P<0.05$), the resistance exercise group ($P<0.001$) and for the combined exercise group ($P<0.001$) after 4 months of exercise training. The activity subsequently increased for all exercise groups and after 8 months it was restored to the pre exercise levels.

After 4 months of exercise training, catalase (CAT) activity, significantly increased for the aerobic exercise group ($P<0.001$), the resistance exercise group ($P<0.05$) and for the combined exercise group ($P<0.05$). After 8 months of exercise training catalase activityremained high for the aerobic and resistance exercise groups but not statistically significant, while in the combined exercise group it remained significantlyelevated ($p<0.05$). At the end of the 1stdetraining period, catalase activity remained high, however, these increases were not statistically significant. Furthermore, at the end of the 2nddetraining period, catalase activity remained significantly elevated for the resistance exercise group ($P<0.05$) and the combined exercise group ($P<0.05$), while for the aerobic exercise group, although it remained high, was not statistically significant. This activity subsequently decreased for all groups, and at the end of the 3rd month of the detraining period it was restored to pre exercise levels.

Table 9b. Biomarkers of oxidative stress in Red Blood Cell Lysate (PC & CAT)

	Training			Detraining	
	Pre	Month 4	Month 8	Month 1	Month 2	Month 3
Protein Carbonyls						
Aerobic	0,659 ± 0,039	0,512* ± 0,053	0,709 ± 0,053	0,691 ± 0,04	0,724 ± 0,054	0,655 ± 0,05
Resistance	0,813 ± 0,049	0,411# ± 0,067	0,782 ± 0,068	0,834 ± 0,051	0,933 ± 0,069	0,699 ± 0,064
Combined	0,815 ± 0,042	0,501# ± 0,058	0,796 ± 0,058	0,848 ± 0,043	0,905 ± 0,059	0,678 ± 0,055
Control	0,712 ± 0,042	0,663 ± 0,058	0,761 ± 0,058	0,716 ± 0,043	0,718 ± 0,059	0,689 ± 0,055
CAT						
Aerobic	16,754 ± 3,065	57,9# ± 8,108	18,354 ± 5,496	20,692 ± 3,15	23,554 ± 2,929	17,077 ± 2,098
Resistance	13,818 ± 3,332	40,964* ± 8,814	19,982 ± 5,975	16,073 ± 3,425	26,209* ± 3,184	18,5 ± 2,281
Combined	14,887 ± 2,853	34,933* ± 7,548	28,053* ± 5,116	21,327 ± 2,933	22,193* ± 2,727	17,413 ± 1,953
Control	18,409 ± 3,332	23,282 ± 8,814	17,8 ± 5,975	19,973 ± 3,425	25,064 ± 3,184	17,655 ± 2,281

* Sig vs. pre in the same group ($p<0.05$)

Sig vs. pre in the same group ($p<0.001$)

V. DISCUSSION

To the best of our knowledge, this is the first study that investigated the effects of three different types of exercise on oxidative stress markers, in CVD patients, for such a long time (i.e. 8months of exercise training and 3 months of detraining). The aim of this study was to determine the effects of aerobic, resistance and combined exercise training, followed by a detraining period on redox status in cardiovascular diseases patients.

It is well known that, oxidative responses play a major role in the pathophysiology of cardiovascular complications. Further, oxidative stress trigger signals, can either directly cause injury to the cardiac tissue or increase the atherosclerotic process (Ramana et al. 2016). However, there is strong evidence that, repeated low level bouts of oxidative stress, up-regulate endogenous antioxidant defense mechanisms, which might paradoxically improve health and longevity in CVD patients.

In addition, the exercise induced oxidative stress might itself be beneficial, by reducing arterial antioxidant enzymes in different tissues: heart, liver, blood, or muscle. Recent evidence suggests that both aerobic and anaerobic exercise training are beneficial to improve redox balance in humans, and any type of exercise training will be beneficial for improving redox balance against potential risk factors of excessive ROS mediated diseases (Park, 2016).

It seems that the aerobic exercise has influenced the most physical fitness and biochemical parameters compared to the other types of exercise. In our study aerobic exercise improved body composition and blood pressure, increased flexibility, muscle strength and VO2max and affected positively and over a longer period of time the most of oxidative stress variables that were assessed. As we expected, resistance exercise training, caused the greatest increases in muscle strength and during the detraining period these favorable effects lasted longer and at higher levels compared tothe aerobic and the combined exercise training. The fact that, muscle strength has remained at higher levels during the detraining period, shows that the strength has contributed to the maintenance of VO2max for a longer period of time after the exercise cessation compared to the aerobic and the combined exercise training. However, during the resistance training programme, the flexibility of lower back and hamstring muscles remained stable, while at the end of the second month of the detraining period it showed a significant decrease. Furthermore, resistance exercise did not affect positively arterial pressure after 4 months of training. Although, systolic blood pressure significantly decreased after 8 months of resistance exercise training, however at

the end of the 1st detraining period it was restored to the baseline values.These results are in accordance with previous studies (Blumenthal et al. 1991; Van Hoof et al. 1996), which have shown that 16 weeks of resistance exercise training, failed to reduce blood pressure in patients with mild hypertension. On the other hand, aerobic and combined exercise training, reduced systolic blood pressure after 4 months of exercise training and remained decreased until the end of the 3rd month of the detraining period. Furthermore, only aerobic exercise training has improved diastolic blood pressure, after 4 months of exercise training and has been maintained until the end of the 3rd month of the detraining period. We suggest that in an intervention training programme for CVD patients, resistance exercise has to be included, however, the type of exercise that has shown to be the most important for these patients is the aerobic exercise. Therefore, we believe that combined exercise is the appropriate type of exercise, but the aerobic exercise has to be the most dominant type of exercise.

An enhanced level of antioxidant protection has been suggested recently (Larsen et al. 2016) as the mechanism underlying the decrease in ROS which, in turn, lowers blood pressure. In our study, although blood pressure remained at low levels during the detraining period, oxidative stress variables that were assessed, were restored to pre exercise values.

Redox status

Aerobic exercise training

The primary novel findings were that aerobic exercise training enhances the antioxidant defensesin CVD patients. In our study, the results have shown that aerobic exercise training affected all biomarkers of oxidative stress in plasma and serum and in red blood cell lysate, at least after 4 month of aerobic exercise training. Furthermore, the results showed that regular AE training, increases the antioxidants in CVD patients such as GSH, TAC, TBARS and CAT, which defend the system against oxidative damage.

More specifically, as we can see from the results above, after 4 months of aerobic exercise training, TAC, GSH, GSH/GSSG and CAT levels were significantly increased, while TBARS, GSSG and PC levels were significantly decreased. After 8 months of aerobic exercise training, TBARS, PC and CAT activity were restored to the pre exercise levels, while TAC, GSH and GSH/GSSG remained elevated. Furthermore, GSSG remained statistically significant ($p<0.05$) at low levels until the end of the 1st detraining period.These results are in accordance with previous studies, which have shown that aerobic exercise training improve antioxidant

capacity (Alghadir et al. 2016; Chis et al. 2015; Tang et al. 2016; Holland et al. 2015; Krause et al. 2014; Coelho et al. 2013).

Resistance exercise training

It has been reported that changes in enzymatic antioxidant defense and inflammatory markers followed by the resistance training are independent of training intensity (Azizbeigi K et al. 2015; Carteri et al. 2015; Flack et al. 2016). According to Atabek and colleagues (Atabek et al. 2015), exercises performed at low intensity may fail to develop adaptation and up-regulation in the antioxidant defense system. Our results have shown that after 4 months of resistance exercise training, TAC and CAT levels were significantly increased, PC levels were decreased and there were no changes in TBARS, GSH, GSSG or GSH/GSSG. After 8 months of resistance exercise training, only TAC remained elevated, while all others biomarkers of oxidative stress wererestored to the pre exercise levels. The intensity of our resistance training protocol, may not be enough to affect all biomarkers of oxidative stress.

Combined exercise training

On the other hand, after 4 months of combined exercise training, TAC and CAT levels were significantly increased and remained elevated until the end of the exercise training period (8months). PC and TBARS levels were decreased after 4 months of combined exercise training, whereas they were restored to the pre exercise levels at the end of the exercise training period (8months). There were no changes in GSH, GSSG or GSH/GSSG with the combined exercise training.

This is in agreement with previous investigations, indicating that combined exercise training induced the same changes on circulating antioxidant capacity and oxidative stress (Azizbeigi, et al. 2014; Soares et al. 2015), however their examination period was 8 weeks and 16 weeks respectively.

Detraining

To date, studies involving animals and humans have provided valuable information on the consequences of detraining. Some consequences of detraining, such as decreased bradycardia at rest, decreased vagal reactivation, deregulation of insulin secretion and glucose concentration, decreased activation of GLUT-4 transporters, modified lipid profile, may considerably among others make the health of CVD patients worse. However, to the

best of our knowledge, there is evidence that sustained effect of exercise training on strength (Coetsee and Terblanche 2015; Yasuda et al. 2015; Fatouros et al. 2005), lipid metabolism (Theodorou et al. 2016; Sertie et al. 2015; Farias et al. 2015), body mass index, functional fitness (Toraman, 2005) and on cardiovascular system (Marini et al. 2008; Carneiro-J_unior et al. 2010; Lehnen et al. 2010), can be maintained for an extended period after training cessation.

In our study, at the end of the 1st detraining period, oxidative stress biomarkers did not show statistically significant differences compared to pre exercise values except from GSSG concentrations. GSSG concentrations in the aerobic exercise group remained statistically significant at low levels. These data signify the important role of exercise in reducing the GSSG and keeping it suppressed for a month after the exercise cessation.

In contrast, the other biomarkers of oxidative stress for all groups restored near the pre exercise values at the end of the 1st detraining period, except catalase activity, which remained high in all exercise groups, however, these increases were not statistically significant. Furthermore, at the end of the 2nd detraining period, catalase activity remained significantly elevated for the resistance exercise group ($P<0.05$) and the combined exercise group ($P<0.05$). Although catalase activity remained high for the aerobic exercise group, this increase was not statistically significant. This activity subsequently decreased for all groups, and at the end of the 3rd month of detraining period, it was restored to the pre exercise levels. Taken together, these results suggest that the beneficial effects of exercise regarding oxidative stress markers are likely to last upto two months after the exercise.

The beneficial effects of exercise training during the detraining period is also reported in previous research which has shown that, 2 weeks of detraining could partially revert the exercise-induced improvements in cardiac hypertrophy, cardiac function, anti-inflammatory cytokine and oxidative stress in the PVN of hypertensive rats, although, positive effects in MAP and PICs remained unchanged. Therefore, Agarwal and colleagues (Agarwal et al. 2012) suggest that, 2 weeks of detraining is not long enough to completely abolish the exercise-induced beneficial effects. However, previous studies reported that, 3-4 months of detraining may lead to complete reversal of the cardio-protection offered by exercise training (Miyahi et al. 2004; Tokmakidis and Volaklis , 2003).

Recently, Theodorou et al. (2016) have shown that the favorable effects of a combined exercise training program not only are maintained after a detraining period, but also lasted longer in the majority of the measured parameters compared with aerobic and resistance

training alone, after exercise cessation. As far as our results are concerned regarding the maintenance of the favorable effects on oxidative stress markers during the detraining period, depends on the type of exercise,which is some indicators are affected by resistance exercise and others by aerobic exercise.

In addition, muscular strength of elderly individuals, when subjected to resistance training of moderate to high intensity, can be maintained above baseline levels during 2 to 31 weeks of detraining (Coetsee and Terblanche 2015; Yasuda et al. 2015; Harris et al. 2007; Fatouros et al. 2005, Taraman 2005).

In addition, at the end of the 2nd month of the detraining period, TAC values for the aerobic exercise group significantly increased ($P<0.05$) and remained increased ($P<0.05$) until the end of the 3rd month of detraining period. The mechanisms involved in this response are unclear and warrant additional research.

Furthermore in the combined exercise group the ratio of GSH/GSSG was significantly decreased ($P<0.05$) at the end of the 3rd detraining period. However, these results need further investigation.

VI. CONCLUSIONS

One of the most frequently examined biomarkers of protein oxidation is plasma protein carbonyl (PC) concentration. Among the oxidative damage markers analyzed in this study, the PC level is considered to be the most significant effect of the exercise training. In our results pc significantly decreased for all exercise groups, however, after 8 months it was restored to the pre exercise levels. More specifically, after 4 months of exercise training, pc significantly decreased for the aerobic exercise group ($P<0.05$), the resistance exercise group ($P<0.001$) and for the combined exercise group ($P<0.001$).

In addition, TBARS were significantly decreased only in the aerobic and combined exercise group, and reduced levels of GSSG were observed only in the aerobic exercise group and remained at low levels until the end of the 1st detraining period. These results suggest that the effect of training on protein oxidation and on lipid peroxidationoccurring in an exerciseprogramme, depend on the type of exercise.

On one hand, it seems that, protein oxidation is more affected when performing resistance exercise rather than aerobic exercise in the CVD patients.On the other hand, the reduced levels of TBARS which were observed only in the aerobic and combined exercise group, suggest that, the lipid peroxidation seems to be affected mainly by the aerobic exercise

training, since in these two groups aerobic exercise is taking place. These results are in accordance with previous research (Sbardelotto et al. 2017), which suggests that the systemic changes related to aging mediated by physical training, depend on the type of training accomplished; *i.e.,* the effects of training vary and occur in an exercise type-dependent manner.

As we can see from the results, TAC levels were significantly increased for all exercise groups, and have been remained elevated during the 8 months of exercise training period. Based on these results, it seems that TAC is the most sensitive variable of the biomarkers of oxidative stress that we have used.

Redox status evaluated by Catalase (CAT) showed more than twofold increase in all exercised groups after 4 month of training. Furthermore, our results concerning of CAT is in agreement with the findings of Camiletti-Moiron and colleagues (Camiletti-Moiron et al. 2015), who have shown that CAT levels increased after 12 weeks of high intensity resistance training protocol in motorized treadmill, however did not alter the other antioxidant enzymes.

In contrast, the results from the present study are in disagreement with some previous studies that failed to find significant differences in markers of oxidative stress following an exercise intervention (Campbell et al. 2010; Wadley et al. 2014). More specifically, Wadley and colleagues (Wadley et al. 2014) have reported that oxidative stress biomarkers have not been changed after 3 months of aerobic exercise training, however our study has shown that the aerobic exercise improves antioxidant capacity and decreases oxidative stress biomarkers.

The reasons for these discrepancies may be due to:

1. different types of exercise stimulus used,
2. different durations of the training and detraining periods,
3. variation in the parameters investigated with some studies assessing changes at a cellular level, others focusing on changes at an organ or functional level, and very few investigating both,
4. variation on the individual age, sex, fitness level and endurance capacity.

In conclusion, the major findings of our study were the following: (a)the improvement of antioxidant capacity through exercise training tends to be maintained up to two months after the exercise cessation; (b) the beneficial effects of exercise on oxidative stress indices

are complete loss one month after the end of the exercise training; (c) protein oxidation is more affected when performing resistance exercise rather than aerobic exercise in the CVD patients; (d) lipid peroxidation seems to be affected mainly by the aerobic exercise training; (f) the type and the intensity of exercise, seem to be decisive for changes in the antioxidant enzymes; (h) it seems that aerobic exercise training is related to higher antioxidant capacity; (i) in an intervention training programme for CVD patients, resistance exercise has to be included, however, the type of exercise that has shown to be the most important for these patients is the aerobic exercise; (j) for better antioxidant status, exercise must be a lifetime commitment.

VII. FUTURE PERSPECTIVES

It is necessary for future studies, to clarify the importance of different modes and amounts/intensities of exercise on oxidative stress in CVD patients. Furthermore, the combination of exercise training program with diet or supplementations, has been found to be more effective than isolated treatments in attenuating atherosclerotic plaque (Napoli C et al. 2006), oxidative stress, Ca2_ homeostasis disruptions, and mitochondrial dysfunctions in the hearts of rats (da Silva et al. 2015; Lee et al. 2014). Future researches on this topic need to focus on the effects of diet plus exercise training on oxidative stress in CVD patients.

In addition, further research is needed in order to determine the effects on oxidative stress markers during a second period of training and detraining, and if the heart is adapted more rapidly indicating this way that cells retain memory of the previous training response, and restore the redox balance.

VIII. REFERENCES

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IX. ANEXX TABLES

Annex table 1: : Percentage changes in biomarkers of oxidative stress in Plasma and Serum (TBARS & TAC)

	Training						Detraining					
	Month 4			Month 8			Month 1			Month 2			Month 3		
TBARS															
Aerobic	-39,30%*	±	0,90	-0,20%	±	0,89	12,74%	±	0,90	7,28%	±	0,92	6,16%	±	0,87
Resistance	-28,37%	±	0,86	-2,89%	±	0,86	21,37%	±	0,87	10,06%	±	0,89	8,83%	±	0,83
Combined	-26,23%*	±	0,91	-3,10%	±	0,90	13,64%	±	0,91	-6,10%	±	0,92	15,43%	±	0,88
Control	-4,67%	±	0,89	2,59%	±	0,89	20,49%	±	0,90	20,37%	±	0,92	13,31%	±	0,87
TAC															
Aerobic	16,99%#	±	0,97	23,73%#	±	0,98	-0,52%	±	0,97	7,98%*	±	0,97	9,43%*	±	0,98
Resistance	23,25%#	±	0,97	20,02%#	±	0,97	0,97%	±	0,96	8,93%	±	0,97	9,36%	±	0,97
Combined	17,45%#	±	0,97	16,45%#	±	0,98	2,81%	±	0,97	4,31%	±	0,97	4,91%	±	0,97
Control	2,82%	±	0,98	3,09%	±	0,98	-2,27%	±	0,97	-3,91%	±	0,98	-7,90%	±	0,98

* Sig vs. pre in the same group ($p<0.05$)

Sig vs. pre in the same group ($p<0.001$)

Annex table 2a: : Percentage changes in biomarkers of oxidative stress in Red Blood Cell Lysate (GSH, GSSG, GSH/GSSG)

	Training						Detraining					
	Month 4			Month 8			Month 1			Month 2			Month 3		
GSH															
Aerobic	34,33%*	±	0,88	34,44%*	±	0,85	-0,52%	±	0,90	-12,84%	±	0,92	-5,65%	±	0,86
Resistance	25,60%	±	0,85	2,47%	±	0,82	-25,35%	±	0,88	-28,55%	±	0,89	-13,53%	±	0,83
Combined	9,76%	±	0,88	-0,69%	±	0,85	-15,46%	±	0,90	-5,94%	±	0,92	-23,90%	±	0,86
Control	2,61%	±	0,89	-18,71%	±	0,86	-15,67%	±	0,91	-13,89%	±	0,92	-18,43%	±	0,87
GSSG															
Aerobic	-19,97%*	±	0,92	-16,60%*	±	0,91	-18,87%*	±	0,92	-4,93%	±	0,94	9,08%	±	0,94
Resistance	3,08%	±	0,88	-2,26%	±	0,87	-8,15%	±	0,88	6,79%	±	0,91	18,66%	±	0,90
Combined	-11,05%	±	0,90	-9,77%	±	0,89	-15,04%	±	0,90	7,39%	±	0,93	11,81%	±	0,92
Control	-3,93%	±	0,91	-4,65%	±	0,90	-3,29%	±	0,91	-0,08%	±	0,93	0,88%	±	0,93
GSH/ GSSG															
Aerobic	95,12%#	±	0,72	56,11%*	±	0,81	9,28%	±	0,87	-8,02%	±	0,88	-12,10%	±	0,87
Resistance	24,07%	±	0,72	-8,73%	±	0,81	-35,60%	±	0,86	-39,75%	±	0,87	-32,23%	±	0,87
Combined	26,01%	±	0,77	12,15%	±	0,84	-7,45%	±	0,89	-17,15%	±	0,90	-36,88%*	±	0,89
Control	4,58%	±	0,73	-2,94%	±	0,82	6,22%	±	0,87	-0,59%	±	0,88	-25,71%	±	0,87

Annex table 2b: : Percentage changes in biomarkers of oxidative stress in Red Blood Cell Lysate (PC, CAT)

	Training						Detraining					
	Month 4			Month 8			Month 1			Month 2			Month 3		
Protein Carbonyls															
Aerobic	-22,31%*	±	0,92	7,59%	±	0,92	4,86%	±	0,94	9,86%%	±	0,92	-0,61%	±	0,92
Resistance	-49,45%#	±	0,92	-3,81%	±	0,92	2,58%	±	0,94	14,76%	±	0,92	-14,02%	±	0,92
Combined	-38,53%#	±	0,93	-2,33%	±	0,93	4,05%	±	0,95	11,04%	±	0,93	-16,81%	±	0,93
Control	-6,88%	±	0,92	6,88%	±	0,92	0,56%	±	0,94	0,84%	±	0,92	-3,23%	±	0,92
CAT															
Aerobic	245,59%#	±	0,52	9,55%	±	0,67	23,50%	±	0,81	40,59%	±	0,83	1,93%	±	0,87
Resistance	196,45%*	±	0,36	44,61%	±	0,57	16,32%	±	0,75	89,67%*	±	0,77	33,88%	±	0,83
Combined	134,65%*	±	0,49	88,44%*	±	0,66	43,26%	±	0,80	49,08%*	±	0,82	16,97%	±	0,87
Control	26,47%	±	0,52	-3,31%	±	0,68	8,50%	±	0,81	36,15%	±	0,83	-4,10%	±	0,88

* Sig vs. pre in the same group ($p<0.05$)

Sig vs. pre in the same group ($p<0.001$)